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(54) Title: *RPS* GENE FAMILY, PRIMERS, PROBES, AND DETECTION METHODS

(57) Abstract

Disclosed is substantially pure DNA encoding an *Arabidopsis thaliana* Rps2 polypeptide; substantially pure Rps2 polypeptide; and methods of using such DNA to express the Rps2 polypeptide in plant cells and whole plants to provide, in transgenic plants, disease resistance to pathogens. Also disclosed are conserved regions characteristic of the RPS family and primers and probes for the identification and isolation of additional RPS disease-resistance genes.

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RPS GENE FAMILY, PRIMERS, PROBES, AND DETECTION METHODS

Statement as to Federally Sponsored Research

This invention was made in part with Government funding and the Government therefore has certain rights in the invention.

Background of the Invention

The invention relates to recombinant plant nucleic acids and polypeptides and uses thereof to confer disease resistance to pathogens in transgenic plants.

Plants employ a variety of defensive strategies to combat pathogens. One defense response, the so-called hypersensitive response (HR), involves rapid localized necrosis of infected tissue. In several host-pathogen interactions, genetic analysis has revealed a gene-for-gene correspondence between a particular avirulence (*avr*) gene in an avirulent pathogen that elicits an HR in a host possessing a particular resistance gene.

Summary of the Invention

In general, the invention features substantially pure DNA (for example, genomic DNA, cDNA, or synthetic DNA) encoding an Rps polypeptide as defined below. In related aspects, the invention also features a vector, a cell (e.g., a plant cell), and a transgenic plant or seed thereof which includes such a substantially pure DNA encoding an Rps polypeptide.

In preferred embodiments, an *RPS* gene is the *RPS2* gene of a plant of the genus *Arabidopsis*. In various preferred embodiments, the cell is a transformed plant cell derived from a cell of a transgenic plant. In related aspects, the invention features a transgenic plant containing a transgene which encodes an Rps

polypeptide that is expressed in plant tissue susceptible to infection by pathogens expressing the *avrRpt2* avirulence gene or pathogens expressing an avirulence signal similarly recognized by an Rps polypeptide.

In a second aspect, the invention features a substantially pure DNA which includes a promoter capable of expressing the *RPS2* gene in plant tissue susceptible to infection by bacterial pathogens expressing the *avrRpt2* avirulence gene.

In preferred embodiments, the promoter is the promoter native to an *RPS* gene. Additionally, transcriptional and translational regulatory regions are preferably native to an *RPS* gene.

The transgenic plants of the invention are preferably plants which are susceptible to infection by a pathogen expressing an avirulence gene, preferably the *avrRpt2* avirulence gene. In preferred embodiments the transgenic plant is from the group of plants consisting of but not limited to *Arabidopsis*, tomato, soybean, bean, maize, wheat and rice.

In another aspect, the invention features a method of providing resistance in a plant to a pathogen which involves: (a) producing a transgenic plant cell having a transgene encoding an Rps2 polypeptide wherein the transgene is integrated into the genome of the transgenic plant and is positioned for expression in the plant cell; and (b) growing a transgenic plant from the transgenic plant cell wherein the *RPS2* transgene is expressed in the transgenic plant.

In another aspect, the invention features a method of detecting a resistance gene in a plant cell involving: (a) contacting the *RPS2* gene or a portion thereof greater than 9 nucleic acids, preferably greater than 18 nucleic acids in length with a preparation of genomic DNA from the plant cell under hybridization conditions providing

detection of DNA sequences having about 50% or greater sequence identity to the DNA sequence of Fig. 2 encoding the Rps2 polypeptide.

In another aspect, the invention features a method of producing an Rps2 polypeptide which involves: (a) providing a cell transformed with DNA encoding an Rps2 polypeptide positioned for expression in the cell; (b) culturing the transformed cell under conditions for expressing the DNA; and (c) isolating the Rps2 polypeptide.

In another aspect, the invention features substantially pure Rps2 polypeptide. Preferably, the polypeptide includes a greater than 50 amino acid sequence substantially identical to a greater than 50 amino acid sequence shown in Fig. 2, open reading frame "a". Most preferably, the polypeptide is the *Arabidopsis thaliana* Rps2 polypeptide.

In another aspect, the invention features a method of providing resistance in a transgenic plant to infection by pathogens which do not carry the *avrRpt2* avirulence gene wherein the method includes: (a) producing a transgenic plant cell having transgenes encoding an Rps2 polypeptide as well as a transgene encoding the *avrRpt2* gene product wherein the transgenes are integrated into the genome of the transgenic plant; are positioned for expression in the plant cell; and the *avrRpt2* transgene and, if desired, the *RPS2* gene, are under the control of regulatory sequences suitable for controlled expression of the gene(s); and (b) growing a transgenic plant from the transgenic plant cell wherein the *RPS2* and *avrRpt2* transgenes are expressed in the transgenic plant.

In another aspect, the invention features a method of providing resistance in a transgenic plant to infection by pathogens in the absence of avirulence gene

expression in the pathogen wherein the method involves: (a) producing a transgenic plant cell having integrated in the genome a transgene containing the *RPS2* gene under the control of a promoter providing constitutive expression of the *RPS2* gene; and (b) growing a transgenic plant from the transgenic plant cell wherein the *RPS2* transgene is expressed constitutively in the transgenic plant.

In another aspect, the invention features a method of providing controllable resistance in a transgenic plant to infection by pathogens in the absence of avirulence gene expression in the pathogen wherein the method involves: (a) producing a transgenic plant cell having integrated in the genome a transgene containing the *RPS2* gene under the control of a promoter providing controllable expression of the *RPS2* gene; and (b) growing a transgenic plant from the transgenic plant cell wherein the *RPS2* transgene is controllably expressed in the transgenic plant. In preferred embodiments, the *RPS2* gene is expressed using a tissue-specific or cell type-specific promoter, or by a promoter that is activated by the introduction of an external signal or agent, such as a chemical signal or agent.

In other aspects, the invention features a substantially pure oligonucleotide including one or a combination of the sequences:

5′ GGNATGGGNGGNNTNGGNAARACNAC 3′, [SEQ ID NO: 158] wherein N is A, T, G, or C; and R is A or G;

5′ NARNGGNARNCC 3′, [SEQ ID NO: 169] wherein N is A, T, G or C; and R is A or G;

5′NCGNGWNGTNAKDAWNCGNGA 3′, [SEQ ID NO: 159] wherein N is A, T, G or C; W is A or T; D is A, G, or T; and K is G or T;

5′ GGWNTBGGWAARACHAC 3′, [SEQ ID NO: 160] wherein N is A, T, G or C; R is G or A; B is C, G, or T; H is A, C, or T; and W is A or T;

5′ TYGAYGAYRTBKRBRA 3′, [SEQ ID NO: 163] wherein R is G or A; B is C, G, or T; D is A, G, or T; Y is T or C; and K is G or T;

5′ TYCCAVAYRTCRTCNA 3′, [SEQ ID NO: 164] wherein N is A, T, G or C; R is G or A; V is G or C or A; and Y is T or C;

5′ GGWYTBCCWYTBGCHYT 3′, [SEQ ID NO: 170] wherein B is C, G, or T; H is A, C, or T; W is A or T; and Y is T or C;

5′ ARDGCVARWGGVARNCC 3′, [SEQ ID NO: 171] wherein N is A, T, G or C; R is G or A; W is A or T; D is A, G, or T; and V is G, C, or A; and

5′ ARRTTRTCRTADSWRAWYTT 3′, [SEQ ID NO: 174] wherein R is G or A; W is A or T; D is A, G, or T; S is G or C; and Y is C or T.

In other aspects, the invention features a recombinant plant gene including one or a combination of the DNA sequences:

5′ GGNATGGGNGGNNTNGGNAARACNAC 3′, [SEQ ID NO: 162] wherein N is A, T, G or C; and R is A or G;

5′ NARNGGNARNCC 3′, [SEQ ID NO: 169] wherein N is A, T, G or C; and R is A or G;

5′ NCGNGWNGTNAKDAWNCGNGA 3′, [SEQ ID NO: 167] wherein N is A, T, G or C; W is A or T; D is A, G or T; and K is G or T.

In another aspect, the invention feaures a substantially pure plant polypeptide including one or a combiantion of the amino acid sequences:

Gly Xaa_1 Xaa_2 Gly Xaa_3 Gly Lys Thr Thr Xaa_4 Xaa_5, [SEQ ID NO: 191] wherein Xaa_1 is Met or Pro; Xaa_2 is Gly or Pro; Xaa_3 is Ile, Leu, or Val; Xaa_4 is Ile, Leu, or Thr; and Xaa_5 is Ala or Met;

Xaa_1 Xaa_2 Xaa_3 Leu Xaa_4 Xaa_5 Xaa_6 Asp Asp Xaa_7 Xaa_8, [SEQ ID NO; 192]
wherein Xaa_1 is Phe or Lys; Xaa_2 is Arg or Lys; Xaa_3 is Ile, Val, or Phe; Xaa_4 is Ile, Leu, or Val; Xaa_5 is Ile or Leu; Xaa_6 is Ile or Val; Xaa_7 is Ile, Leu, or Val; and Xaa_8 is Asp or Trp;

Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Thr Xaa_6 Arg, [SEQ ID NO: 193]
wherein Xaa_1 is Ser or Cys; Xaa_2 is Arg or Lys; Xaa_3 is Phe, Ile, or Val; Xaa_4 is Ile, or Met; Xaa_5 is Ile, Leu, or Phe; Xaa_6 is Ser, Cys, or Thr;

Gly Leu Pro Leu Xaa_1 Xaa_2 Xaa_3 Xaa_4, [SEQ ID NO.: 194]
wherein Xaa_1 is Thr, Ala, or Ser; Xaa_2 is Leu or Val; Xaa_3 is Ile, Val, or Lys; and Xaa_4 is Val or Thr; and

Xaa_1 Xaa_2 Ser Tyr Xaa_3 Xaa_4 Leu, [SEQ ID NO: 195]
wherein Xaa_1 is Lys or Gly; Xaa_2 is Ile or Phe; Xaa_3 is Asp or Lys; and Xaa_4 is Ala, Gly, or Asn.

In another aspect, the invention features a method of isolating a disease-resistance gene or fragment thereof from a plant cell, involving: (a) providing a sample of plant cell DNA; (b) providing a pair of oligonucleotides having sequence homology to a conserved region of an RPS disease-resistance gene; (c) combining the pair of oligonucleotides with the plant cell DNA sample under conditions suitable for polymerase chain reaction-mediated DNA amplification; and (d) isolating the amplified disease-resistance gene or fragment thereof.

In preferred embodiments, the amplification is carried out using a reverse-transcription polymerase chain reaction, for example, the RACE method

In another aspect, the invention features a method of identifying a plant disease-resistance gene in a plant cell, involving: (a) providing a preparation of plant cell DNA (for example, from the plant genome); (b) providing a detectably-labelled DNA sequence (for example, prepared by the methods of the invention) having homology to a conserved region of an RPS gene; (c) contacting the preparation of plant cell DNA with the detectablly-labelled DNA sequence under hybridization conditions providing detection of genes having 50% or greater sequence identity; and (d) identifying a disease-resistance gene by its association with the detectable label.

In another aspect, the invention features a method of isolating a disease-resistance gene from a recombinant plant cell library, involving: (a) providing a recombinant plant cell library; (b) contacting the recombinant plant cell library with a detectably-labelled gene fragment produced according to the PCR method of the invention under hybridization conditions providing detection of genes having 50% or greater sequence identity; and (c) isolating a member of a disease-resistance gene by its association with the detectable label.

In anotehr aspect, the invention features a method of isolating a disease-resistance gene from a recombinant plant cell library, involving: (a) providing a recombinant plant cell library; (b) contacting the recombinant plant cell library with a detectably-labelled RPS oligonucleotide of the invention under hybridization conditions providing detection of genes having 50% or greater sequence identity; and (c) isolating a disease-

resistance gene by its association with the detectable label.

In another aspect, the invention features a recombinant plant polypeptide capable of conferring disease-resistance wherein the plant polypeptide includes a P-loop domain or nucleotide binding site domain. Preferably, the polypeptide further includes a leucine-rich repeating domain.

In another aspect, the invention features a recombinant plant polypeptide capable of conferring disease-resistance wherein the plant polypeptide contains a leucine-rich repeating domain.

In anotehr aspect, the invention features a plant disease-resistance gene isolated according to the method involving: (a) providing a sample of plant cell DNA; (b) providing a pair of oligonucleotides having sequence homology to a conserved region of an RPS disease-resistance gene; (c) combining the pair of oligonucleotides with the plant cell DNA sample under conditions suitable for polymerase chain reaction-mediated DNA amplification; and (d) isolating the amplified disease-resistance gene or fragment thereof.

In another aspect, the invention features a plant disease-resistance gene isolated according to the method involving: (a) providing a preparation of plant cell DNA; (b) providing a detectably-labelled DNA sequence having homology to a conserved region of an RPS gene; (c) contacting the preparation of plant cell DNA with the detectably-labelled DNA sequence under hybridization conditions providing detection of genes having 50% or greater sequence identity; and (d) identifying a disease-resistance gene by its association with the detectable label.

In another aspect, the invention features a plant disease-resistance gene according to the method

involving: (a) providing a recombinant plant cell library; (b) contacting the recombinant plant cell library with a detectably-labelled RPS gene fragment produced according to the method of the invention under hybridization conditions providing detection of genes having 50% or greater sequence identity; and (c) isolating a disease-resistance gene by its association with the detectable label.

In another aspect, the invention features a method of identifying a plant disease-resistance gene involving: (a) providing a plant tissue sample; (b) introducing by biolistic transformation into the plant tissue sample a candidate plant disease-resistance gene; (c) expressing the candidate plant disease-resistance gene within the plant tissue sample; and (d) determining whether the plant tissue sample exhibits a disease-resistance response, whereby a response identifies a plant disease-resistance gene.

Preferably, the plant tissue sample is either leaf, root, flower, fruit, or stem tissue; the candidate plant disease-resistance gene is obtained from a cDNA expression library; and the disease-resistance response is the hypersensitive response.

In another aspect, the invention features a plant disease-resistance gene isolated according to the method involving: (a) providing a plant tissue sample; (b) introducing by biolistic transformation into the plant tissue sample a candidate plant disease-resistance gene; (c) expressing the candidate plant disease-resistance gene within the plant tissue sample; and (d) determining whether the plant tissue sample exhibits a disease-resistance response, whereby a response identifies a plant disease-resistance gene.

In another aspect, the invention features a purified antibody which binds specifically to an rps

family protein. Such an antibody may be used in any standard immunodetection method for the identification of an RPS polypeptide.

In another aspect, the invention features a DNA sequence substantially identical to the DNA sequence shown in Figure 12.

In another aspect, the invention features a substantially pure polypeptide having a sequence substantially identical to a Prf amino acid sequence shown in Figure 5 (A or B).

By "disease resistance gene" is meant a gene encoding a polypeptide capable of triggering the plant defense response in a plant cell or plant tissue. An *RPS* gene is a disease resistance gene having about 50% or greater sequence identity to the *RPS2* sequence of Fig. 2 or a portion thereof. The gene, *RPS2*, is a disease resistance gene encoding the Rps2 disease resistance polypeptide from *Arabidopsis thaliana*.

By "polypeptide" is meant any chain of amino acids, regardless of length or post-translational modification (e.g., glycosylation or phosphorylation).

By "substantially identical" is meant a polypeptide or nucleic acid exhibiting at least 50%, preferably 85%, more preferably 90%, and most preferably 95% homology to a reference amino acid or nucleic acid sequence. For polypeptides, the length of comparison sequences will generally be at least 16 amino acids, preferably at least 20 amino acids, more preferably at least 25 amino acids, and most preferably 35 amino acids. For nucleic acids, the length of comparison sequences will generally be at least 50 nucleotides, preferably at least 60 nucleotides, more preferably at least 75 nucleotides, and most preferably 110 nucleotides.

Sequence identity is typically measured using sequence analysis software (e.g., Sequence Analysis

Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705). Such software matches similar sequences by assigning degrees of homology to various substitutions, deletions, substitutions, and other modifications. Conservative substitutions typically include substitutions within the following groups: glycine alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid, asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine.

By a "substantially pure polypeptide" is meant an Rps2 polypeptide which has been separated from components which naturally accompany it. Typically, the polypeptide is substantially pure when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the preparation is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, Rps2 polypeptide. A substantially pure Rps2 polypeptide may be obtained, for example, by extraction from a natural source (e.g., a plant cell); by expression of a recombinant nucleic acid encoding an Rps2 polypeptide; or by chemically synthesizing the protein. Purity can be measured by any appropriate method, e.g., those described in column chromatography, polyacrylamide gel electrophoresis, or by HPLC analysis.

A protein is substantially free of naturally associated components when it is separated from those contaminants which accompany it in its natural state. Thus, a protein which is chemically synthesized or produced in a cellular system different from the cell from which it naturally originates will be substantially free from its naturally associated components. Accordingly, substantially pure polypeptides include

those derived from eukaryotic organisms but synthesized in *E. coli* or other prokaryotes.

By "substantially pure DNA" is meant DNA that is free of the genes which, in the naturally-occurring genome of the organism from which the DNA of the invention is derived, flank the gene. The term therefore includes, for example, a recombinant DNA which is incorporated into a vector; into an autonomously replicating plasmid or virus; or into the genomic DNA of a prokaryote or eukaryote; or which exists as a separate molecule (e.g., a cDNA or a genomic or cDNA fragment produced by PCR or restriction endonuclease digestion) independent of other sequences. It also includes a recombinant DNA which is part of a hybrid gene encoding additional polypeptide sequence.

By "transformed cell" is meant a cell into which (or into an ancestor of which) has been introduced, by means of recombinant DNA techniques, a DNA molecule encoding (as used herein) an Rps2 polypeptide.

By "positioned for expression" is meant that the DNA molecule is positioned adjacent to a DNA sequence which directs transcription and translation of the sequence (i.e., facilitates the production of, e.g., an Rps2 polypeptide, a recombinant protein or a RNA molecule).

By "reporter gene" is meant a gene whose expression may be assayed; such genes include, without limitation, β-glucuronidase (GUS), luciferase, chloramphenicol transacetylase (CAT), and ß-galactosidase.

By "promoter" is meant minimal sequence sufficient to direct transcription. Also included in the invention are those promoter elements which are sufficient to render promoter-dependent gene expression controllable for cell-type specific, tissue-specific or inducible by

external signals or agents; such elements may be located in the 5′ or 3′ regions of the native gene.

By "operably linked" is meant that a gene and a regulatory sequence(s) are connected in such a way as to permit gene expression when the appropriate molecules (e.g., transcriptional activator proteins) are bound to the regulatory sequence(s).

By "plant cell" is meant any self-propagating cell bounded by a semi-permeable membrane and containing a plastid. Such a cell also requires a cell wall if further propagation is desired. Plant cell, as used herein includes, without limitation, algae, cyanobacteria, seeds suspension cultures, embryos, meristematic regions, callus tissue, leaves, roots, shoots, gametophytes, sporophytes, pollen, and microspores.

By "transgene" is meant any piece of DNA which is inserted by artifice into a cell, and becomes part of the genome of the organism which develops from that cell. Such a transgene may include a gene which is partly or entirely heterologous (i.e., foreign) to the transgenic organism, or may represent a gene homologous to an endogenous gene of the organism.

By "transgenic" is meant any cell which includes a DNA sequence which is inserted by artifice into a cell and becomes part of the genome of the organism which develops from that cell. As used herein, the transgenic organisms are generally transgenic plants and the DNA (transgene) is inserted by artifice into the nuclear or plastidic genome.

By "pathogen" is meant an organism whose infection into the cells of viable plant tissue elicits a disease response in the plant tissue.

By an "RPS disease-resistance gene" is meant any member of the family of plant genes characterized by their ability to trigger a plant defense response and

having at least 20%, preferably 30%, and most preferably 50% amino acid sequence identity to one of the conserved regions of one of the RPS members described herein (i.e., either the RPS2, L6, N, or Prf genes). Representative members of the RPS gene family include, without limitation, the rps2 gene of *Arabidopsis*, the L6 gene of flax, the Prf gene of tomato, and the N gene of tobacco.

By "conserved region" is meant any stretch of six or more contiguous amino acids exhibiting at least 30%, preferably 50%, and most preferably 70% amino acid sequence identity between two or more of the RPS family members, RPS2, L6, N, or Prf. Examples of preferred conserved regions are shown (as boxed or designated sequences) in Figures 5 A and B, 6, 7, and 8 and include, without limitation, nucleotide binding site domains, leucine-rich repeats, leucine zipper domains, and P-loop domains.

By "detectably-labelled" is meant any means for marking and identifying the presence of a molecule, e.g., an oligonucleotide probe or primer, a gene or fragment thereof, or a cDNA molecule. Methods for detectably-labelling a molecule are well known in the art and include, without limitation, radioactive labelling (e.g., with an isotope such as ^{32}P or ^{35}S) and nonradioactive labelling (e.g., chemiluminescent labelling, e.g., fluorescein labelling).

By "biolistic transformation" is meant any method for introducing foreign molecules into a cell using velocity driven microprojectiles such as tungsten or gold particles. Such velocity-driven methods originate from pressure bursts which include, but are not limited to, helium-driven, air-driven, and gunpowder-driven techniques. Biolistic transformation may be applied to the transformation or transfection of a wide variety of cell types and intact tissues including, without

limitation, intracellular organelles (e.g., chloroplasts and mitochondria), bacteria, yeast, fungi, algae, pollen, animal tissue, plant tissue (e.g., leaf, seedling, embryo, epidermis, flower, meristem, and root), pollen, and cultured cells.

By "purified antibody" is meant antibody which is at least 60%, by weight, free from proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the preparation is at least 75%, more preferably 90%, and most preferably at least 99%, by weight, antibody, e.g., an rps2-specific antibody. A purified rps antibody may be obtained, for example, by affinity chromatography using recombinantly-produced rps protein or conserved motif peptides and standard techniques.

By "specifically binds" is meant an antibody which recognizes and binds an rps protein but which does not substantially recognize and bind other molecules in a sample, e.g., a biological sample, which naturally includes rps protein.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Detailed Description

The drawings will first be described.

Drawings

Figs. 1A - 1F are a schematic summary of the physical and RFLP analysis that led to the cloning of the *RPS2* locus.

Fig. 1A is a diagram showing the alignment of the genetic and the RFLP maps of the relevant portion of *Arabidopsis thaliana* chromosome IV adapted from the map published by Lister and Dean (1993) Plant J. 4:745-750.

The RFLP marker L11F11 represents the left arm of the YUP11F11 YAC clone.

Fig. 1B is a diagram showing the alignment of relevant YACs around the *RPS2* locus. YAC constructs designated YUP16G5, YUP18G9 and YUP11F11 were provided by J. Ecker, University of Pennsylvania. YAC constructs designated EW3H7, EW11D4, EW11E4, and EW9C3 were provided by E. Ward, Ciba-Geigy, Inc.

Fig. 1C is a diagram showing the alignment of cosmid clones around the *RPS2* locus. Cosmid clones with the designation H are derivatives of the EW3H7 YAC clone whereas those with the designation E are derivatives of the EW11E4 YAC clone. Vertical arrows indicate the relative positions of RFLP markers between the ecotypes La-er and the *rps2-101N* plant. The RFLP markers were identified by screening a Southern blot containing more than 50 different restriction enzyme digests using either the entire part or pieces of the corresponding cosmid clones as probes. The cosmid clones described in Fig. 1C were provided by J. Giraudat, C.N.R.S., Gif-sur-Yvette, France.

Figs. 1D and 1E are maps of *Eco*RI restriction endonuclease sites in the cosmids E4-4 and E4-6, respectively. The recombination break points surrounding the *RPS2* locus are located within the 4.5 and 7.5 kb *Eco*RI restriction endonuclease fragments.

Fig. 1F is a diagram showing the approximate location of genes which encode the RNA transcripts which have been identified by polyA$^+$ RNA blot analysis. The sizes of the transcripts are given in kilobase pairs below each transcript.

Fig. 2 [SEQ ID NOS; 1-104, 196-201] is the complete nucleotide sequence of cDNA-4 comprising the *RPS2* gene locus. The three reading frames are shown below the nucleotide sequence. The deduced amino acid

sequence of reading frame "a" is provided and contains 909 amino acids. The methionine encoded by the ATG start codon is circled in open reading frame "a" of Fig. 2. The A of the ATG start codon is nucleotide 31 of Fig. 2.

Fig. 3 [SEQ ID NOS: 105-106] is the nucleotide sequence of the *avrRpt2* gene and its deduced amino acid sequence. A potential ribosome binding site is underlined. An inverted repeat is indicated by horizontal arrows at the 3' end of the open reading frame. The deduced amino acid sequence is provided below the nucleotide sequence of the open reading frame.

Fig. 4 is a schematic summary of the complementation analysis that allowed functional confirmation that the DNA carried on p4104 and p4115 (encoding cDNA-4) confers *RPS2* disease resistance activity to *Arabidopsis thaliana* plants previously lacking *RPS2* disease resistance activity. Small vertical marks along the "genome" line represent restriction enzyme *Eco*RI recognition sites, and the numbers above this line represent the size, in kilobase pairs (kb), of the resulting DNA fragments (see also Fig. 1E). Opposite "cDNAs" are the approximate locations of the coding sequences for RNA transcripts (See also Fig. 1F); arrowheads indicate the direction of transcription for cDNAs 4, 5, and 6. For functional complementation experiments, *rps2-201C/rps2-201C* plants were genetically transformed with the *Arabidopsis thaliana* genomic DNA sequences indicated; these sequences were carried on the named plasmids (derivatives of the binary cosmid vector pSLJ4541) and delivered to the plant via *Agrobacterium*-mediated transformation methods. The disease resistance phenotype of the resulting transformants following inoculation with *P. syringae* expressing *avrRpt2* is given as "Sus." (susceptible, no resistance response) or "Res." (disease resistant).

Fig. 5A [SEQ ID NOS: 107-136;, AND 142] shows regions of sequence similarity between the L-6 protein of flax, N protein of tobacco, Prf protein of tomato, and rps2 protein of *Arabidopsis*.

Fig. 5B [SEQ ID NOS: 107, 108, 137-140] shows sequence similarity between the N and L-6 proteins.

Fig. 6 [SEQ ID NOS: 141 and 142] shows a sequence analysis of RPS2 polypeptide showing polypeptide regions corresponding to an N-terminal hydrophobic region, a leucine zipper, NBSs (kinase-1a, kinase-2, and kinase-3 motifs), and a predicted membrane integrated region.

Fig. 7 [SEQ ID NOS: 143-146 shows the amino acid sequence of the RPS2 LRR (amino acids 505-867). The top line indicates the consensus sequences for the *RPS2* LRR. An "X" stands for an arbitrary amino acid sequence and an "a" stands for an aliphatic amino acid residue. The consensus sequence for the *RPS2* LRR is closely related to the consensus for the yeast adenylate cyclase CYR1 LRR (PX Xa XXL XXL XXLXL XXNXaXXa). The amino acid residues that match the consensus sequence are shown in bold. Although this figure shows 14 LRRs, the C-terminal boundary of the LRR is not very clear because the LRR closer to the C-terminus does not fit the consensus sequence very well.

Fig. 8 [SEQ ID NO: 3] shows a sequence analysis of RPS2, indicating regions with similarity to leucine zipper, P-loop, membrane-spanning, and leucine-rich repeat motifs. Regions with similarity to defined functional domains are indicated with a line over the relevant amino acids. Potential N-glycosylation sequences are marked with a dot, and the location of the rps2-201 Thr to Pro mutation at animo acid 668 is marked with an asterisk.

Fig. 9 is a schematic representation of the transient assay method. The top panel shows the

essential principles of the assay. The bottom panel shows a schematic representation of the actual transient assay procedure. *Psp* NP53121 is used because it is a weak *Arabidopsis* pathogen, but potent in causing the HR when carrying an avirulence gene. In the absence of an HR, the damage to plant cells infected with NP53121 is minimal, enhancing the difference of GUS accumulation in cells that undergo the HR in comparison to those that do not. Prior to bombardment, one half of an *Arabidopsis* leaf is infiltrated with P. syringae (stippled side of leaf); the other half of the leaf serves as a noninfected control, an "internal" reference for the infected side, and as a measure of transformation efficiency.

Fig. 10, panels A-B, are photographs showing the complementation of the rps2 mutant phenotype using the biolistic transient expression assay. The left sides of rps2-101C mutant leaves were infiltrated with Psp 3121/avrRpt2. Infiltrated leaves were cobombarded with either 35S-uidA plus ΔGUS (Panel A) or 35S-uidA plus 35S-RPS2 (cDNA-2 clone 4) (Panel B). Note that in Panel B the infected side of the leaf shows less GUS activity than the uninfected side, indicating that the transformed cells on the infected side underwent an HR and that 35S-RPS2 complemented the mutant phenotype (see Fig. 9).

Fig. 11 is a schematic representation of pKEx4tr showing the structure of this cDNA expression vector. For convenience, the multiple cloning site contains the 8bp recognition sequences for PmeI and NotI and is flanked by T7 and T3 promoters. The region spanning the modified 35S promoter to the nopaline synthase 3' sequences (nos 3') was cloned into the Hind III-EcoRI site of pUC18, resulting in the loss of the EcoRI site.

Fig. 12 shows a nucleic acid sequence of the tomato Prf gene.

The Genetic Basis for Resistance to Pathogens

An overview of the interaction between a plant host and a microbial pathogen is presented. The invasion of a plant by a potential pathogen can have a range of outcomes delineated by the following outcomes: either the pathogen successfully proliferates in the host, causing associated disease symptoms, or its growth is halted by the host defenses. In some plant-pathogen interactions, the visible hallmark of an active defense response is the so-called hypersensitive response or "HR". The HR involves rapid necrosis of cells near the site of the infection and may include the formation of a visible dry brown lesion. Pathogens which elicit an HR on a given host are said to be avirulent on that host, the host is said to be resistant, and the plant-pathogen interaction is said to be incompatible. Strains which proliferate and cause disease on a particular host are said to be virulent; in this case the host is said to be susceptible, and the plant-pathogen interaction is said to be compatible

"Classical" genetic analysis has been used successfully to help elucidate the genetic basis of plant-pathogen recognition for those cases in which a series of strains (races) of a particular fungal or bacterial pathogen are either virulent or avirulent on a series of cultivars (or different wild accessions) of a particular host species. In many such cases, genetic analysis of both the host and the pathogen revealed that many avirulent fungal and bacterial strains differ from virulent ones by the possession of one or more avirulence (*avr*) genes that have corresponding "resistance" genes in the host. This avirulence gene-resistance gene correspondence is termed the "gene-for-gene" model (Crute, et al., (1985) pp 197-309 in: *Mechanisms of Resistance to Plant Disease*. R.S.S. Fraser, ed.;

Ellingboe, (1981) Annu. Rev. Phytopathol. 19:125-143; Flor, (1971) Annu. Rev. Phytopathol. 9:275-296; Keen and Staskawicz, (1988) supra; and Keen et al. in: *Application of Biotechnology to Plant Pathogen Control*. I. Chet, ed., John Wiley & Sons, 1993, pp. 65-88). According to a simple formulation of this model, plant resistance genes encode specific receptors for molecular signals generated by *avr* genes. Signal transduction pathway(s) then carry the signal to a set of target genes that initiate the HR and other host defenses (Gabriel and Rolfe, (1990) Annu. Rev. Phytopathol. 28:365-391). Despite this simple predictive model, the molecular basis of the *avr*-resistance gene interaction is still unknown.

One basic prediction of the gene-for-gene hypothesis has been convincingly confirmed at the molecular level by the cloning of a variety of bacterial *avr* genes (Innes, et al., (1993) J. Bacteriol. 175:4859-4869; Dong, et al., (1991) Plant Cell 3:61-72; Whelan et al., (1991) Plant Cell 3:49-59; Staskawicz et al., (1987) J. Bacteriol. 169:5789-5794; Gabriel et al., (1986) P.N.A.S., USA 83:6415-6419; Keen and Staskawicz, (1988) Annu. Rev. Microbiol. 42:421-440; Kobayashi et al., (1990) Mol. Plant-Microbe Interact. 3:94-102 and (1990) Mol. Plant-Microbe Interact. 3:103-111). Many of these cloned avirulence genes have been shown to correspond to individual resistance genes in the cognate host plants and have been shown to confer an avirulent phenotype when transferred to an otherwise virulent strain. The *avrRpt2* locus was isolated from *Pseudomonas syringae* pv. *tomato* and sequenced by Innes et al. (Innes, R. et al. (1993) J. Bacteriol. 175:4859-4869). Fig. 3 is the nucleotide sequence and deduced amino acid sequence of the *avrRpt2* gene.

Examples of known signals to which plants respond when infected by pathogens include harpins from *Erwinia*

(Wei et al. (1992) Science 257:85-88) and *Pseudomonas* (He et al. (1993) Cell 73:1255-1266); *avr4* (Joosten et al. (1994) Nature 367:384-386) and avr9 peptides (van den Ackerveken et al (1992) Plant J. 2:359-366) from *Cladosporium*; *PopA1* from *Pseudomonas* (Arlat et al. (1994) EMBO J. 13:543-553); avrD-generated lipopolysaccharide (Midland et al. (1993) J. Org. Chem. 58:2940-2945); and *NIP1* from *Rhynchosporium* (Hahn et al. (1993) Mol. Plant-Microbe Interact. 6:745-754).

Compared to *avr* genes, considerably less is known about plant resistance genes that correspond to specific *avr*-generated signals. The plant resistance gene, *RPS2* (rps for resistance to Pseudomonas syringae), the first gene of a new, previously unidentified class of plant disease resistance genes corresponds to a specific *avr* gene (*avrRpt2*). Some of the work leading up to the cloning of *RPS2* is described in Yu, et al., (1993), Molecular Plant-Microbe Interactions 6:434-443 and in Kunkel, et al., (1993) Plant Cell 5:865-875.

An apparently unrelated avirulence gene which corresponds specifically to plant disease resistance gene, *Pto*, has been isolated from tomato (*Lycopersicon esculentum*)(Martin et al., (1993) Science 262:1432-1436). Tomato plants expressing the *Pto* gene are resistant to infection by strains of *Pseudomonas syringae* pv. *tomato* that express the *avrPto* avirulence gene. The amino acid sequence inferred from the *Pto* gene DNA sequence displays strong similarity to serine-threonine protein kinases, implicating *Pto* in signal transduction. No similarity to the tomato *Pto* locus or any known protein kinases was observed for *RPS2*, suggesting that *RPS2* is representative of a new class of plant disease resistance genes.

The isolation of a race-specific resistance gene from *Zea mays* (corn) known as *Hm1* has been reported (Johal and Briggs (1992) Science 258:985-987). *Hm1*

confers resistance against specific races of the fungal pathogen *Cochliobolus carbonum* by controlling degradation of a fungal toxin, a strategy that is mechanistically distinct from the avirulence-gene specific resistance of the *RPS2-avrRpt2* resistance mechanism.

The cloned *RPS2* gene of the invention can be used to facilitate the construction of plants that are resistant to specific pathogens and to overcome the inability to transfer disease resistance genes between species using classical breeding techniques (Keen et al., (1993), supra). There now follows a description of the cloning and characterization of an *Arabidopsis thaliana* *RPS2* genetic locus, the *RPS2* genomic DNA, and the *RPS2* cDNA. The *avrRpt2* gene and the *RPS2* gene, as well as mutants *rps2-101C*, *rps2-102C*, and *rps2-201C* (also designated *rps2-201*), are described in Dong, et al., (1991) Plant Cell 3:61-72; Yu, et al., (1993) supra; Kunkel et al., (1993) supra; Whalen et al., (1991), supra; and Innes et al., (1993), supra). A mutant designated *rps2-101N* has also been isolated. The identification and cloning of the *RPS2* gene is described below.

RPS2 Overcomes Sensitivity to Pathogens Carrying the avrRpt2 Gene

To demonstrate the genetic relationship between an avirulence gene in the pathogen and a resistance gene in the host, it was necessary first to isolate an avirulence gene. By screening *Pseudomonas* strains that are known pathogens of crop plants related to *Arabidopsis*, highly virulent strains, *P. syringae* pv. *maculicola (Psm)* ES4326, *P. syringae* pv. *tomato* (*Pst*) DC3000, and an avirulent strain, *Pst* MM1065 were identified and analyzed as to their respective abilities to grow in wild type *Arabidopsis thaliana* plants (Dong *et al.*, (1991) Plant

Cell, 3:61-72; Whalen et al., (1991) Plant Cell 3:49-59; MM1065 is designated JL1065 in Whalen et al.). *Psm* ES4326 or *Pst* DC3000 can multiply 10^4 fold in *Arabidopsis thaliana* leaves and cause water-soaked lesions that appear over the course of two days. *Pst* MM1065 multiplies a maximum of 10 fold in *Arabidopsis thaliana* leaves and causes the appearance of a mildly chlorotic dry lesion after 48 hours. Thus, disease resistance is associated with severely inhibited growth of the pathogen.

An avirulence gene (*avr*) of the *Pst* MM1065 strain was cloned using standard techniques as described in Dong *et al*. (1991), Plant Cell 3:61-72; Whalen et al., (1991) supra; and Innes et al., (1993), supra. The isolated avirulence gene from this strain was designated *avrRpt2*. Normally, the virulent strain *Psm* ES4326 or *Pst* DC3000 causes the appearance of disease symptoms after 48 hours as described above. In contrast, *Psm* ES4326/*avrRpt2* or *Pst* DC3000/*avrRpt2* elicits the appearance of a visible necrotic hypersensitivity response (HR) within 16 hours and multiplies 50 fold less than *Psm* ES4326 or *Pst* DC3000 in wild type *Arabidopsis thaliana* leaves (Dong *et al*., (1991), supra; and Whalen et al., (1991), supra). Thus, disease resistance in a wild type *Arabidopsis* plant requires, in part, an avirulence gene in the pathogen or a signal generated by the avirulence gene.

The isolation of four *Arabidopsis thaliana* disease resistance mutants has been described using the cloned *avrRpt2* gene to search for the host gene required for disease resistance to pathogens carrying the *avrRpt2* gene (Yu et al., (1993), supra; Kunkel et al., (1993), supra). The four *Arabidopsis thaliana* mutants failed to develop an HR when infiltrated with *Psm* ES4326/*avrRpt2* or *Pst* DC3000/*avrRpt2* as expected for plants having lost their disease resistance capacity. In the case of one of these

mutants, approximately 3000 five to six week old M_2 ecotype Columbia (Col-0 plants) plants generated by ethyl methanesulfonic acid (EMS) mutagenesis were hand-inoculated with *Psm* ES4326/*avrRpt2* and a single mutant, *rps2-101C*, was identified (resistance to Pseudomonas syringae) (Yu *et al.*, (1993), supra).

The second mutant was isolated using a procedure that specifically enriches for mutants unable to mount an HR (Yu *et al.*, (1993), supra). When 10-day old *Arabidopsis thaliana* seedlings growing on petri plates are infiltrated with *Pseudomonas syringae* pv. *phaseolicola* (*Psp*) NPS3121 versus *Psp* NPS3121/*avrRpt2*, about 90% of the plants infiltrated with *Psp* NPS3121 survive, whereas about 90%-95% of the plants infiltrated with *Psp* NPS3121/*avrRpt2* die. Apparently, vacuum infiltration of an entire small *Arabidopsis thaliana* seedling with *Psp* NPS3121/*avrRpt2* elicits a systemic HR which usually kills the seedling. In contrast, seedlings infiltrated with *Psp* NPS3121 survive because *Psp* NPS3121 is a weak pathogen on *Arabidopsis thaliana*. The second disease resistance mutant was isolated by infiltrating 4000 EMS-mutagenized Columbia M_2 seedlings with *Psp* NPS3121/*avrRpt2*. Two hundred survivors were obtained. These were transplanted to soil and re-screened by hand inoculation when the plants reached maturity. Of these 200 survivors, one plant failed to give an HR when hand-infiltrated with *Psm* ES4326/*avrRpt2*. This mutant was designated *rps2-102C* (Yu *et al.*, (1993), supra).

A third mutant, *rps2-201C*, was isolated in a screen of approximately 7500 M_2 plants derived from seed of *Arabidopsis thaliana* ecotype Col-0 that had been mutagenized with diepoxybutane (Kunkel et al., (1993), supra). Plants were inoculated by dipping entire leaf rosettes into a solution containing *Pst* DC3000/*avrRpt2* bacteria and the surfactant Silwet L-77 (Whalen et al.,

(1991), supra), incubating plants in a controlled environment growth chamber for three to four days, and then visually observing disease symptom development. This screen revealed four mutant lines (carrying the *rps2-201C*, *rps2-202C*, *rps2-203C*, and *rps2-204C* alleles), and plants homozygous for *rps2-201C* were a primary subject for further study (Kunkel et al., (1993), supra and the instant application).

Isolation of the fourth *rps2* mutant, *rps2-101N*, has not yet been published. This fourth isolate is either a mutant or a susceptible *Arabidopsis* ecotype. Seeds of the *Arabidopsis* Nossen ecotype were gamma-irradiated and then sown densely in flats and allowed to germinate and grow through a nylon mesh. When the plants were five to six weeks old, the flats were inverted, the plants were partially submerged in a tray containing a culture of *Psm* ES4326/*avrRpt2*, and the plants were vacuum infiltrated in a vacuum desiccator. Plants inoculated this way develop an HR within 24 hours. Using this procedure, approximately 40,000 plants were screened and one susceptible plant was identified. Subsequent RFLP analysis of this plant suggested that it may not be a Nossen mutant but rather a different *Arabidopsis* ecotype that is susceptible to *Psm* ES4326/*avrRpt2*. This plant is referred to as *rps2-101N*. The isolated mutants *rps2-101C*, *rps2-102C*, *rps2-201C*, and *rps2-101N* are referred to collectively as the "*rps2* mutants".

The *rps2* Mutants Fail to Specifically Respond to the Cloned Avirulence Gene, *avrRpt2*

The *RPS2* gene product is specifically required for resistance to pathogens carrying the avirulence gene, *avrRpt2*. A mutation in Rps2 polypeptide that eliminates or reduces its function would be observable as the absence of a hypersensitive response upon infiltration of

the pathogen. The *rps2* mutants displayed disease symptoms or a null response when infiltrated with *Psm* ES4326/*avrRpt2*, *Pst* DC3000/*avrRpt2* or *Psp* NPS3121/*avrRpt2*, respectively. Specifically, no HR response was elicited, indicating that the plants were susceptible and had lost resistance to the pathogen despite the presence of the *avrRpt2* gene in the pathogen.

Pathogen growth in *rps2* mutant plant leaves was similar in the presence and absence of the *avrRpt2* gene. *Psm* ES4326 and *Psm* ES4326/*avrRpt2* growth in *rps2* mutants was compared and found to multiply equally well in the *rps2* mutants, at the same rate that *Psm* Es4326 multiplied in wild-type *Arabidopsis* leaves. Similar results were observed for *Pst* DC3000 and *Pst* DC3000/*avrRpt2* growth in *rps2* mutants.

The *rps2* mutants displayed a HR when infiltrated with *Pseudomonas* pathogens carrying other *avr* genes, *Psm* ES4326/*avrB*, *Pst* DC3000/*avrB*, *Psm* ES4326/*avrRpm1*, *Pst* DC3000/*avrRpm1*. The ability to mount an HR to an *avr* gene other than *avrRpt2* indicates that the *rps2* mutants isolated by selection with *avrRpt2* are specific to *avrRpt2*.

Mapping and Cloning of the *RPS2* Gene

Genetic analysis of *rps2* mutants *rps2-101C*, *rps2-102C*, *rps-201C* and *rps-101N* showed that they all corresponded to genes that segregated as expected for a single Mendelian locus and that all four were most likely allelic. The four *rps2* mutants were mapped to the bottom of chromosome IV using standard RFLP mapping procedures including polymerase chain reaction (PCR)-based markers (Yu *et al.*, (1993), supra; Kunkel *et al.*, (1993), supra; and Mindrinos, M., unpublished). Segregation analysis showed that *rps2-101C* and *rps2-102C* are tightly linked to the PCR marker, PG11, while the RFLP marker M600 was used

to define the chromosome location of the *rps2-201C* mutation (Fig. 1A) (Yu *et al.*, (1993), supra; Kunkel *et al.*, (1993), supra). *RPS2* has subsequently been mapped to the centromeric side of PG11.

Heterozygous *RPS2/rps2* plants display a defense response that is intermediate between those displayed by the wild-type and homozygous *rps2/rps2* mutant plants (Yu, et al., (1993), supra; and Kunkel et al., (1993), supra). The heterozygous plants mounted an HR in response to *Psm* ES4326/*avrRpt2* or *Pst* DC3000/*avrRpt2* infiltration; however, the HR appeared later than in wild type plants and required a higher minimum inoculum (Yu, et al., (1993), supra; and Kunkel et al., (1993), supra).

High Resolution Mapping of the *RPS2* Gene and *RPS2* cDNA Isolation

To carry out map-based cloning of the *RPS2* gene, *rps2-101N/rps2-101N* was crossed with Landsberg *erecta* *RPS2/RPS2*. Plants of the F_1 generation were allowed to self pollinate (to "self") and 165 F_2 plants were selfed to generate F_3 families. Standard RFLP mapping procedures showed that *rps2-101N* maps close to and on the centromeric side of the RFLP marker, PG11. To obtain a more detailed map position, *rps2-101N/rps-101N* was crossed with a doubly marked Landsberg *erecta* strain containing the recessive mutations, *cer2* and *ap2*. The genetic distance between *cer2* and *ap2* is approximately 15 cM, and the *rps2* locus is located within this interval. F_2 plants that displayed either a *CER2 ap2* or a *cer2 AP2* genotype were collected, selfed, and scored for *RPS2* by inoculating at least 20 F_3 plants for each F_2 with *Psm* ES4326/*avrRpt2*. DNA was also prepared from a pool of approximately 20 F_3 plants for each F_2 line. The *CER2 ap2* and *cer2 AP2* recombinants were used to carry out a chromosome walk that is illustrated in Figure 1.

As shown in Figure 1, *RPS2* was mapped to a 28-35 kb region spanned by cosmid clones E4-4 and E4-6. This region contains at least six genes that produce detectable transcripts. There were no significant differences in the sizes of the transcripts or their level of expression in the *rps2* mutants as determined by RNA blot analysis. cDNA clones of each of these transcripts were isolated and five of these were sequenced. As is described below, one of these transcripts, cDNA-4, was shown to correspond to the *RPS2* locus. From this study, three independent cDNA clones (cDNA-4-4, cDNA-4-5, and cDNA-4-11) were obtained corresponding to *RPS2* from Columbia ecotype wild type plants. The apparent sizes of *RPS2* transcripts were 3.8 and 3.1 kb as determined by RNA blot analysis.

A fourth independent cDNA-4 clone (cDNA-4-2453) was obtained using map-based isolation of *RPS2* in a separate study. Yeast artificial chromosome (YAC) clones were identified that carry contiguous, overlapping inserts of *Arabidopsis thaliana* ecotype Col-O genomic DNA from the M600 region spanning approximately 900 kb in the *RPS2* region. *Arabidopsis* YAC libraries were obtained from J. Ecker and E. Ward, supra and from E. Grill (Grill and Somerville (1991) Mol. Gen. Genet. 226:484-490). Cosmids designated "H" and "E" were derived from the YAC inserts and were used in the isolation of *RPS2* (Fig. 1).

The genetic and physical location of *RPS2* was more precisely defined using physically mapped RFLP, RAPD (random amplified polymorphic DNA) and CAPS (cleaved amplified polymorphic sequence) markers. Segregating populations from crosses between plants of genotype *RPS2/RPS2* (No-O wild type) and *rps2-201/rps2-201* (Col-O background) were used for genetic mapping. The *RPS2* locus was mapped using markers 17B7LE, PG11, M600 and other markers. For high-resolution genetic mapping, a

set of tightly linked RFLP markers was generated using insert end fragments from YAC and cosmid clones (Fig. 1) (Kunkel et al. (1993), supra; Konieczny and Ausubel (1993) Plant J. 4:403-410; and Chang et al. (1988) PNAS USA 85:6856-6860). Cosmid clones E4-4 and E4-6 were then used to identify expressed transcripts (designated cDNA-4, -5, -6, -7, -8 of Fig 1F) from this region, including the cDNA-4-2453 clone.

RPS2 DNA Sequence Analysis

DNA sequence analysis of cDNA-4 from wild-type Col-0 plants and from mutants *rps2-101C*, *rps2-102C*, *rps2-201C* and *rps2-101N* showed that cDNA-4 corresponds to *RPS2*. DNA sequence analysis of *rps2-101C*, *rps2-102C* and *rps2-201C* revealed changes from the wild-type sequence as shown in Table 1. The numbering system in Table 1 starts at the ATG start codon encoding the first methionine where A is nucleotide 1. DNA sequence analysis of cDNA-4 corresponding to mutant *rps2-102C* showed that it differed from the wild type sequence at amino acid residue 476. Moreover, DNA sequence analysis of the cDNA corresponding to cDNA-4 from *rps2-101N* showed that it contained a 10 bp insertion at amino acid residue 581, a site within the leucine-rich repeat region which causes a shift in the *RPS2* reading frame. Mutant *rps2-101C* contains a mutation that leads to the formation of a chain termination codon. The DNA sequence of mutant allele *rps2-201C* revealed a mutation altering a single amino acid within a segment of the LRR region that also has similarity to the helix-loop-helix motif, further supporting the designation of this locus as the *RPS2* gene. The DNA and amino acid sequences are shown in Figure 2.

Table 1

Mutant	Wild type	position of mutation	Change
rps2-101C	703 TGA 705	704	TAA Stop Codon
rps2-101N	1741 GTG 1743	1741	GTGGAGTTGTATG Insertion
rps2-102C	1426 AGA 1428 arg	1427	AAA Amino acid 476 lys
rps2-201C	2002 ACC 2004 thr	2002	CCC Amino acid pro

DNA sequence analysis of cDNA-4 corresponding to *RPS2* from wild-type Col-O plants revealed an open reading frame (between two stop codons) spanning 2,751 bp. There are 2,727 bp between the first methionine codon of this reading frame and the 3'-stop codon, which corresponds to a deduced 909 amino acid polypeptide (See open reading frame "a" of Fig. 2). The amino acid sequence has a relative molecular weight of 104,460 and a pI of 6.51.

As discussed below, *RPS2* belongs to a new class of disease resistance genes; the structure of the Rps2 polypeptide does not resemble the protein structure of the product of the previously cloned and publicized avirulence gene-specific plant disease resistance gene, *Pto*, which has a putative protein kinase domain. From the above analysis of the deduced amino acid sequence, *RPS2* contains several distinct protein domains conserved in other proteins from both eukaryotes and prokaryotes. These domains include, but are not limited, to Leucine Rich Repeats (LRR) (Kobe and Deisenhofer, (1994) Nature 366:751-756); nucleotide binding site, e.g. the kinase 1a motif (P-loop) (Saraste et al. (1990) Trends in Biological Sciences TIBS 15:430-434; Helix-Loop-Helix (Murre et al. (1989) Cell 56:777-783; and Leucine Zipper

(Rodrigues and Park (1993) Mol. Cell Biol. 13:6711-6722). The amino acid sequence of Rps2 contains a LRR motif (LRR motif from amino acid residue 505 to amino acid residue 867), which is present in many known proteins and which is thought to be involved in protein-protein interactions and may thus allow interaction with other proteins that are involved in plant disease resistance. The N-terminal portion of the Rps2 polypeptide LRR is, for example, related to the LRR of yeast (*Saccharomyces cerevisiae*) adenylate cyclase, CYR1. A region predicted to be a transmembrane spanning domain (Klein et al. (1985) Biochim., Biophys. Acta 815:468-476) is located from amino acid residue 350 to amino acid residue 365, N-terminal to the LRR. An ATP/GTP binding site motif (P-loop) is predicted to be located between amino acid residue 177 and amino acid residue 194, inclusive. The motifs are discussed in more detail below.

From the above analysis of the deduced amino acid sequence, the Rps2 polypeptide may have a membrane-receptor structure which consists of an N-terminal extracellular region and a C-terminal cytoplasmic region. Alternatively, the topology of the Rps2 may be the opposite: an N-terminal cytoplasmic region and a C-terminal extracellular region. LRR motifs are extracellular in many cases and the Rps2 LRR contains five potential N-glycosylation sites.

Identification of *RPS2* by Functional Complementation

Complementation of *rps2-201* homozygotes with genomic DNA corresponding to *Arabidopsis thaliana* functionally confirmed that the genomic region encoding cDNA-4 carries *RPS2* activity. Cosmids were constructed that contained overlapping contiguous sequences of wild type *Arabidopsis thaliana* DNA from the *RPS2* region contained in YACs EW11D4, EW9C3, and YUP11F1 of Fig. 1

and Fig. 4. The cosmid vectors were constructed from pSLJ4541 (obtained from J. Jones, Sainsbury Institute, Norwich, England) which contains sequences that allow the inserted sequence to be integrated into the plant genome via *Agrobacterium*-mediated transformation (designated "binary cosmid"). "H" and "E" cosmids (Fig. 1) were used to identify clones carrying DNA from the *Arabidopsis thaliana* genomic *RPS2* region.

More than forty binary cosmids containing inserted *RPS2* region DNA were used to transform *rps2-201* homozygous mutants utilizing *Agrobacterium*-mediated transformation (Chang et al. ((1990) p. 28, Abstracts of the Fourth International Conference on *Arabidopsis* Research, Vienna, Austria). Transformants which remained susceptible (determined by methods including the observed absence of an HR following infection to *P. syringae* pv. *phaseolicola* strain 3121 carrying *avrRpt2* and Psp 3121 without *avrRpt2*) indicated that the inserted DNA did not contain functional *RPS2*. These cosmids conferred the "Sus." or susceptible phenotype indicated in Fig. 4. Transformants which had acquired *avrRpt2*-specific disease resistance (determined by methods including the display of a strong hypersensitive response (HR) when inoculated with *Psp* 3121 with *avrRpt2*, but not following inoculation with *Psp* 3121 without *avrRpt2*) suggested that the inserted DNA contained a functional *RPS2* gene capable of conferring the "Res." or resistant phenotype indicated in Fig. 4. Transformants obtained using the pD4 binary cosmid displayed a strong resistance phenotype as described above. The presence of the insert DNA in the transformants was confirmed by classical genetic analysis (the tight genetic linkage of the disease resistance phenotype and the kanamycin resistance phenotype conferred by the cotransformed selectable marker) and Southern analysis. These results indicated that *RPS2* is

encoded by a segment of the 18 kb *Arabidopsis thaliana* genomic region carried on cosmid pD4 (Fig. 4).

To further localize the *RPS2* locus and confirm its ability to confer a resistance phenotype on the *rps2-201* homozygous mutants, a set of six binary cosmids containing partially overlapping genomic DNA inserts were tested. The overlapping inserts pD2, pD4, pD14, pD15, pD27, and pD47 were chosen based on the location of the transcription corresponding to the five cDNA clones in the *RPS2* region (Fig. 4). These transformation experiments utilized a vacuum infiltration procedure (Bechtold et al. (1993) C.R. Acad. Sci. Paris 316:1194-1199) for *Agrobacterium*-mediated transformation. *Agrobacterium*-mediated transformations with cosmids pD2, pD14, pD15, pD39, and pD46 were performed using a root transformation/regeneration protocol (Valveekens et al. (1988), PNAS 85:5536-5540). The results of pathogen inoculation experiments assaying for *RPS2* activity in these transformants is indicated in Fig. 4.

These experiments were further confirmed using a modification of the vacuum filtration procedure. In particular, the procedure of Bechtold et al. (supra) was modified such that plants were grown in peat-based potting soil covered with a screen, primary inflorescences were removed, and plants with secondary inflorescences (approximately 3 to 15 cm in length) were inverted directly into infiltration medium, infiltrated, and then grown to seed harvest without removal from soil (detailed protocol available on the AAtDB computer database (43). The presence of introduced sequences in the initial pD4 transformant was verified by DNA blot analysis with a pD4 vector and insert sequences (separately) as probes. The presence of the expected sequences in transformants obtained with the vacuum infiltration protocol was also confirmed by DNA blot

analysis. Root transformation experiments (19) were performed with an easily regenerable *rps2-201/rps2-201* x No-0 mapping population. Transformants were obtained for pD4 with in plant transformation, for pD2, 14, 16, 39, and 49 with root transformation, and for pD2, 4, 14, 15, 27, and 47 with vacuum infiltration as modified.

Additional transformation experiments utilized binary cosmids carrying the complete coding region and more than 1 kb of upstream genomic sequence for only cDNA-4 or cDNA-6. Using the vacuum infiltration transformation method, three independent transformants were obtained that carried the wild-type cDNA-6 genomic region in a *rps2-201c* homozygous background (pAD431 of Fig. 4). None of these plants displayed *avrRpt2*-dependent disease resistance. Homozygous *rps2-201c* mutants were transformed with wild-type genomic cDNA-4 (p4104 and p4115, each carrying Col-0 genomic sequences corresponding to all of the cDNA-4 open reading frame, plus approximately 1.7 kb of 5′ upstream sequence and approximately 0.3 kb of 3′ sequence downstream of the stop codon). These p4104 and p4115 transformants displayed a disease resistance phenotype similar to the wild-type *RPS2* homozygotes from which the *rps2* were derived. Additional mutants (*rps2-101N* and *rps2-101C* homozygotes) also displayed *avrRpt2*-dependent resistance when transformed with the cDNA-4 genomic region.

RPS2 Sequences Allow Detection of Other Resistance Genes

DNA blot analysis of *Arabidopsis thaliana* genomic DNA using *RPS2* cDNA as the probe showed that *Arabidopsis* contains several DNA sequences that hybridize to *RPS2* or a portion thereof, suggesting that there are several related genes in the *Arabidopsis* genome.

From the aforementioned description and the nucleic acid sequence shown in Fig. 2, it is possible to

isolate other plant disease resistance genes having about 50% or greater sequence identity to the *RPS2* gene. Detection and isolation can be carried out with an oligonucleotide probe containing the *RPS2* gene or a portion thereof greater than 9 nucleic acids in length, and preferably greater than about 18 nucleic acids in length. Probes to sequences encoding specific structural features of the Rps2 polypeptide are preferred as they provide a means of isolating disease resistance genes having similar structural domains. Hybridization can be done using standard techniques such as are described in Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley & Sons, (1989).

For example, high stringency conditions for detecting the *RPS2* gene include hybridization at about 42°C, and about 50% formamide; a first wash at about 65°C, about 2X SSC, and 1% SDS; followed by a second wash at about 65°C and about 0.1% x SSC. Lower stringency conditions for detecting *RPS* genes having about 50% sequence identity to the *RPS2* gene are detected by, for example, hybridization at about 42°C in the absence of formamide; a first wash at about 42°C, about 6X SSC, and about 1% SDS; and a second wash at about 50°C, about 6X SSC, and about 1% SDS. An approximately 350 nucleotide DNA probe encoding the middle portion of the LRR region of Rps2 was used as a probe in the above example. Under lower stringency conditions, a minimum of 5 DNA bands were detected in *Bam*HI digested *Arabidopsis thaliana* genomic DNA as sequences having sufficient sequence identity to hybridize to DNA encoding the middle portion of the LRR motif of Rps2. Similar results were obtained using a probe containing a 300 nucleotide portion of the *RPS2* gene encoding the extreme N-terminus of Rps2 outside of the LRR motif.

Isolation of other disease resistance genes is performed by PCR amplification techniques well known to those skilled in the art of molecular biology using oligonucleotide primers designed to amplify only sequences flanked by the oligonucleotides in genes having sequence identity to *RPS2*. The primers are optionally designed to allow cloning of the amplified product into a suitable vector.

The RPS Disease-Resistance Gene Family

As discussed above, we have discovered that the *Arabidopsis RPS2* gene described herein is representative of a new class of plant resistance genes. Analysis of the derived amino acid sequence for *RPS2* revealed several regions of similarity with known polypeptide motifs (see, e.g., Schneider et al., Genes Dev. 6:797 (1991)). Most prominent among these is a region of multiple, leucine-rich repeats (LRRs). The LRR motif has been implicated in protein-protein interactions and ligand binding in a diverse array of proteins (see, e.g., Kornfield et al., Annu. Rev. Biochem. 64:631 (1985); Alber, Curr. Opin. Gen. Dev. 2:205 (1992); Lupas et al., Science 252:116 2 (1991); Saraste et al., Trend Biochem. Sci. 15:430 (1990)). In one example, LRRs form the hormone binding sites of mammalian gonadotropin hormone receptors (see, e.g, Lupas et al., Science 252:1162 (1991)) and, in another example, a domain of yeast adenylate cyclase that interacts with the RAS2 protein (Kornfield et al., Annu. Rev. Biochem. 64:631 (1985)). In *RPS2*, the LRR domain spans amino acids 503-867 and contains fourteen repeat units of length 22-26 amino acids. A portion of each repeat resembles the LRR consensus sequence (I/L/V)XXLXXLXX(I/L)XL. In Figure 7, the LRRs from *RPS2* are shown, as well as an *RPS2* consensus sequence. Within the *RPS2* LRR region, five (of six) sequences matching the

N-glycosylation consensus sequence [NX(S/T)] were observed (Figure 8, marked with a dot). In particular, N-glycosylation is predicted to occur at amino acids 158, 543, 666, 757, 778, 787. Interestingly, the single nucleotide difference between functional *RPS2* and mutant allele *rps2-201* is within the LRR coding region, and this mutation disrupts one of the potential glycosylation sites.

Also observed in the deduced amino acid sequence for *RPS2* is a second potential protein-protein interaction domain, a leucine zipper (see, e.g., von Heijne, J. Mol. Biol. 225:487 (1992)), at amino acids 30-57. This region contains four contiguous heptad repeats that match the leucine zipper consensus sequence (I/R)XDLXXX. Leucine zippers facilitate the dimerization of transcription factors by formation of coiled-coil structures, but no sequences suggestive of an adjacent DNA binding domain (such as a strongly basic region or a potential zinc-finger) were detected in *RPS2*. Coiled-coil regions also promote specific interactions between proteins that are not transcription factors (see, e.g., Ward et al., Plant Mol. Biol. 14:561 (1990); Ecker, Methods 1:186 (1990); Grill et al., Mol. Gen. Genet. 226:484 (1991)), and computer database similarity searches with the region spanning amino acids 30-57 of *RPS2* revealed highest similarity to the coiled-coil regions of numerous myosin and paramyosin proteins.

A third *RPS2* motif was found at the sequence GPGGVGKT at deduced amino acids 182-189. This portion of *RPS2* precisely matches the generalized consensus for the phosphate-binding loop (P-loop) of numerous ATP- and GTP-binding proteins (see, e.g., Saraste et al., supra)). The postulated *RPS2* P-loop is similar to those found in RAS proteins and ATP synthase β-subunits (Saraste et al., supra), but surprisingly is most similar to the published

P-loop sequences for the *nifH* and *chvD* genes, respectively. The presence of this P-loop sequence strongly suggests nucleotide triphosphate binding as one aspect of *RPS2* function. This domain is also referred to as a kinase-1a motif (or a nucleotide binding site, or NBS). Other conserved NBSs are present in the *RPS2* sequence; these NBSs include a kinase-2 motif at amino acids 258-262 and a kinase-3a motif at amino acids 330-335.

Finally, inspection of the *RPS2* sequence reveals a fourth *RPS2* motif, a potential membrane-spanning domain located at amino acids 340-360. Within this region, a conserved GLPLAL motif is found at amino acids 347-352. The presence of the membrane-spanning domain raises the possibility that the *RPS2* protein is membrane localized, with the N-terminal leucine zipper and P-loop domains residing together on the opposite side of the membrane from the LRR region. An orientation in which the C-terminal LRR domain is extracellular is suggested by the fact that five of the six potential N-linked glycosylation sites occur C-terminal to the proposed membrane-spanning domain, as well as by the overall more positive charge of the N-terminal amino acid residues (see, e.g., Kornfield et al., supra; von Heijne, supra). A number of proteins that contain LRRs are postulated or known to be membrane-spanning receptors in which the LRRs are displayed extracellularly as a ligand-binding domain (see, e.g., Lopez et al., Proc. Natl. Acad. Sci. 84:5615 (1987); Braun et al., EMBO J. 10:1885 (1991); Schneider et al., supra).

The plant kingdom contains hundreds of resistance genes that are necessarily divergent since they control different resistance specificities. However, plant defense responses such as production of activated oxygen species, PR-protein gene expression, and the

hypersensitive response are common to diverse plant-pathogen interactions. This implies that there are points of convergence in the defense signal transduction pathways downstream of initial pathogen recognition, and also suggests that similar functional motifs may exist among diverse resistance gene products. Indeed, *RPS2* is dissimilar from previously described disease resistance genes such as *Hm1* or *Pto* (see, e.g., Johal et al., supra; Martin et al., supra), and thus represents a new class of genes having disease resistance capabilities.

Isolation of Other Members of the RPS Disease-Resistance Gene Family Using Conserved Motif Probes and Primers

We have discovered that the *RPS2* motifs described above are conserved in other disease-resistance genes, including, without limitation, the N protein, the L6 protein, and the Prf protein. As shown in Fig. 5(A and B), we have determined that the L6 polypeptide of flax, the N polypeptide of tobacco, and the Prf polypeptide of tomato each share unique regions of similarity (including, but not limited to, the leucine-rich repeats, the membrane-spanning domain, the leucine zipper, and the P-loop and other NBS domains).

On the basis of this discovery, the isolation of virtually any member of the RPS gene family is made possible using standard techniques. In particular, using all or a portion of the amino acid sequence of a conserved RPS motif (for example, the amino acid sequences defining any RPS P-loop, NBS, leucine-rich repeat, leucine zipper, or membrane-spanning region), one may readily design RPS oligonucleotide probes, including RPS degenerate oligonucleotide probes (i.e., a mixture of all possible coding sequences for a given amino acid sequence). These oligonucleotides may be based upon the sequence of either strand of the DNA comprising the

motif. General methods for designing and preparing such probes are provided, for example, in Ausubel et al., supra and *Guide to Molecular Cloning Techniques*, 1987, S. L. Berger and A. R. Kimmel, eds., Academic Press, New York. These oligonucleotides are useful for RPS gene isolation, either through their use as probes capable of hybridizing to RPS complementary sequences or as primers for various polymerase chain reaction (PCR) cloning strategies.

Hybridization techniques and procedures are well known to those skilled in the art and are described, for example, in Ausubel et al., supra and *Guide to Molecular Cloning Techniques*, 1987, S. L. Berger and A. R. Kimmel, eds., Academic Press, New York. If desired, a combination of different oligonucleotide probes may be used for the screening of the recombinant DNA library. The oligonucleotides are labelled with ^{32}P using methods known in the art, and the detectably-labelled oligonucleotides are used to probe filter replicas from a recombinant plant DNA library. Recombinant DNA libraries may be prepared according to methods well known in the art, for example, as described in Ausubel et al., supra. Positive clones may, if desired, be rescreened with additional oligonucleotide probes based upon other RPS conserved regions. For example, an RPS clone identified based on hybridization with a P-loop-derived probe may be confirmed by re-screening with a leucine-rich repeat-derived oligonucleotide.

As discussed above, RPS oligonucleotides may also be used as primers in PCR cloning strategies. Such PCR methods are well known in the art and described, for example, in PCR Technology, H.A. Erlich, ed., Stockton Press, London, 1989; PCR Protocols: A Guide to Methods and Applications, M.A. Innis, D.H. Gelfand, J.J. Sninsky, and T.J. White, eds., Academic Press, Inc., New York,

1990; and Ausubel et al., supra. If desired, members of the RPS disease-resistance gene family may be isolated using the PCR "RACE" technique, or Rapid Amplification of cDNA Ends (see, e.g., Innis et al., supra). By this method, oligonucleotide primers based on an RPS conserved domain are oriented in the 3′ and 5′ directions and are used to generate overlapping PCR fragments. These overlapping 3′- and 5′-end RACE products are combined to produce an intact full-length cDNA. This method is described in Innis et al., supra; and Frohman et al., Proc. Natl. Acad. Sci. 85:8998, 1988.

Any number of probes and primers according to the invention may be designed based on the conserved RPS motifs described herein. Preferred motifs are boxed in the sequences shown in Fig. 5(A or B). In particular, oligonucleotides according to the invention may be based on the conserved P-loop domain, the amino acids of which are shown below:

MOTIF 1

L6	G MGGIGKTTTA [SEQ ID NO: 110]
N	G MGGVGKTTIA [SEQ ID NO: 111]
PrfP	G MPGLGKTTLA [SEQ ID NO: 112]
RPS2	G PGGVGKTTLM [SEQ ID NO: 113]

From these sequences, appropriate oligonucleotides are designed and prepared using standard methods. Particular examples of RPS oligonucleotides based on the P-loop domain are as follows (N is A, C, T, or G).

Based on MOTIF 1:

5′ GGNATGGGNGGNNTNGGNAA(A or G)ACNAC 3′ [SEQ ID NO: 158]

5′ NCGNG(A/T)NGTNA(T/G)(G/A/T)A(T/A)NCGNA 3′ [SEQ ID NO: 159]

5′ GG(T or A)NT(T or G or C)GG(T or A)AA(G or A)AC(T or C or A)AC 3′ [SEQ ID NO: 160]

5′ GGNATGGGNGGNNTNGGNAA(A or G)ACNAC 3′ [SEQ ID NO: 158]

5′ N(G or A)(C or T)N(A or G)(A or G or T)NGTNGT(C or T)TTNCCNANNCCN(G or L)(G or C)N(G or A)(T or G)NCC 3′[SEQ ID NO: 161]

5′ GGN(C or A)(T or C)N(G or C)(G or C)NGGNNTNGGNAA (A or G)ACNAC 3′[SEQ ID NO: 162]

Other conserved *RPS* motifs useful for oligonucleotide design are shown below. These motifs are also depicted in the sequence of Fig. 5(A or B).

<u>MOTIF 2</u>		
L6	FKILVV LDDVD	[SEQ ID NO: 114]
N	KKVLIV LDDID	[SEQ ID NO: 115]
PrfP	KRFLIL IDDVW	[SEQ ID NO: 116]
RPS2	KRFLLL LDDVW	[SEQ ID NO: 117]
<u>MOTIF 3</u>		
L6	SRFIIT SR	[SEQ ID NO: 118]
N	SRIIIT TR	[SEQ ID NO: 119]
PrfP	SRIILT TR	[SEQ ID NO: 120]
RPS2	CKVMFT TR	[SEQ ID NO: 121]
<u>MOTIF 4</u>		
L6	GLPLTLK V	[SEQ ID NO: 122]
N	GLPLALK V	[SEQ ID NO: 123]
PrfP	GLPLSVV L	[SEQ ID NO: 124]
RPS2	GLPLALI T	[SEQ ID NO: 125]
<u>MOTIF 5</u>		
L6	KISYDAL	[SEQ ID NO: 126]
N	KISYDGL	[SEQ ID NO: 127]
PrfP	GFSYKNL	[SEQ ID NO: 128]
RPS2	KFSYDNL	[SEQ ID NO: 129]

From the above motifs and the sequence motifs designated in Figure 5A and B, appropriate oligonucleotides are designed and prepared. Particular examples of such RPS oligonucleotides are as follows (N is A, T, C, or G).

Based on MOTIF 2:

5′ T(T or C)GA(T or C)GA(T or C)(A or G)T(T or G or C)(T or G)(A or G)(T or G or C)(G or A)A 3′ [SEQ ID NO: 163]

5′ T(T or C)CCA(G or C or A)A(T or C)(G or A)TC(A or G)TCNA 3′ [SEQ ID NO: 164]

5′ (C or G or A)(T or C)(C or A)NA(T or C)(G or A)TC(G or A)TCNA(G or A or T)NA(G or A or C)NANNA(G or A)NA 3′[SEQ ID NO: 165]

5′ (T or A)(T or A)N(A or C)(A or G)(A or G)(T or G or A)TN(T or C)TNNTN(G or T or C)TN(A or T or C)TNGA(T or C)GA 3′[SEQ ID NO: 166]

Based on MOTIF 3:

5′ NCGNG(A or T)NGTNA(T or G)(G or A or T)A(T or A)NCGNGA 3′[SEQ ID NO: 167]

5′ NCGNG(A or T)NGTNA(T or G)(G or A or T)A(T or A)NCGNGA 3′[SEQ ID NO: 167]

5′ NC(G or T)N(G or C)(A or T)NGTNA(A or G or T)(A or G or T)AT(A or G or T)AATNG 3′[SEQ ID NO: 168].

Based on MOTIF 4:

5′ NA(G or A)NGGNA(G or A)NCC 3′[SEQ ID NO: 169]

5′ GG(T or A)(T or C)T(T or G or C)CC(T or A)(T or C)T(T or G or C)GC(T or C or A)(T or C)T 3′[SEQ ID NO: 170]

5′ A(A or G)(T or G or A)GC(G or C or A)A(G or A)(T or A)GG(G or C or A)A(G or A)(A or G or T or C)C C 3′ [SEQ ID NO: 171]

5′ NA(G or A)NGGNA(G or A)NCC 3′ [SEQ ID NO: 169]

5′ N(A or G)NN(T or A)(T or C)NA(G or C or A)N(C or G)(A or T or C)NA(G or A)NGGNA(G or A)NCC 3′ [SEQ ID NO: 172]

5′ GGN(T or C)TNCCN(T or C)TN(G or A or T)(C or G)N(T or G or C)T 3′ [SEQ ID NO: 173]

Based on MOTIF 5:

5′ A(A or G)(A or G)TT(A or G)TC(A or G)TA(G or A or T)(G or C)(T or A)(G or A)A(T or A)(C or T)TT 3′ [SEQ ID NO: 174]

5′ A(G or A)N(T or C)(T or C)NT(C or T)(A or G)TAN(G or C)(A or G)NANN(C or T)(C or T) 3′ [SEQ ID NO: 175]

5′ (G or A)(G or A)N(A or T)T(A or C or T)(T or A)(G or C)NTA(T or C)(G or A)AN(A or G)(A or C or G)N(T or C)T 3′ [SEQ ID NO: 176]

Based on MOTIF 6:

5′ GTNTT(T or C)(T or C)TN(T or A)(G or C)NTT(T or C)(A or C)G(A or G)GG 3′ [SEQ ID NO: 177]

Based on MOTIF 7:

5′ CCNAT(A or C or T)TT(T or C)TA(T or C)(G or A)(T or A)(G or T or C)GTNGA(T or C)CC 3′ [SEQ ID NO: 178]

Based on MOTIF 8:

5′ GTNGGNAT(A or C or T)GA(T or C)(G or A)(A or C)NCA 3′ [SEQ ID NO: 179]

Based on MOTIF 9:

5′ (G or A)AA(G or A)CANGC(A or G or T)AT(G or A)TCNA(G or A)(G or A)AA 3′ [SEQ ID NO: 180]

5′ TT(T or C)(T or C)TNGA(T or C)AT(A or C or T)GCNTG(T or C)TT 3′ [SEQ ID NO: 181]

Based on MOTIF 10:

5′ CCCAT(G or A)TC(T or C)(T or C)(T or G)NA(T or G or A)N(T or A)(G or A)(G or A)TC(A or G)TGCAT 3′ [SEQ ID NO: 182]

5′ ATGCA(T or C)GA(T or C)(T or C)(T or A)N(A or C or T)TN(A or C)(A or G)(A or G)GA(T or C)ATGGG 3′ [SEQ ID NO: 183]

Based on MOTIF 11:

5′ NA(G or A)N(G or C)(A or T)(T or C)T(T or C)NA(A or G)(C or T)TT 3′ [SEQ ID NO: 184]

5′ (A or T)(G or C)NAA(A or G)(T or C)TN(A or G)A(A or G)(A or T)(G or C)N(T or C)T 3′ [SEQ ID NO: 185]

Based on MOTIF 12:

5′ (A or G or T)(A or T)(A or T)(C or T)TCNA(G or A)N(G or C)(A or T)N(T or C)(G or T)NA(G or A) NCC 3′ [SEQ ID NO: 186]

5′ GGN(T or C)TN(A or C)(G or A)N(A or T)(G or L)N(T or C)TNGA 3′ [SEQ ID NO: 187]

Once a clone encoding a candidate RPS family gene is identified, it is then determined whether such gene is capable of conferring disease-resistance to a plant host using the methods described herein or other methods well known in the art of molecular plant pathology.

A Biolistic Transient Expression Assay For Identification of Plant Resistance Genes

We have developed a functional transient expression system capable of providing a rapid and broadly applicable method for identifying and characterizing virtually any gene for its ability to confer disease-resistance to a plant cell. In brief, the assay system involves delivering by biolistic transformation a candidate plant disease-resistance gene to a plant tissue sample (e.g., a piece of tissue from a leaf) and then evaluating the expression of the gene within the tissue by appraising the presence or absence of a disease-resistance response (e.g., the hypersensitive response). This assay provides a method for identifying disease-resistance genes from a wide variety of plant species, including ones that are not amenable to genetic or transgenic studies.

The principle of the assay is depicted in the top portion of Figure 9. In general, plant cells carrying a mutation in the resistance gene of interest are utilized. Prior to biolistic transformation, the plant tissue is infiltrated with a phytopathogenic bacterium carrying the corresponding avirulence gene. In addition, a gene to be assayed for its resistance gene activity is co-introduced by biolistics with a reporter gene. The expression of the cobombarded reporter gene serves as an indicator for viability of the transformed cells. Both genes are expressed under the control of a strong and constitutive promoter. If the gene to be assayed does not complement the resistance gene function, the plant cells do not undergo a hypersensitive response (HR) and, therefore, survive (Fig. 9, top panel, right). In this case, cells accumulate a large amount of the reporter gene product. If, on the other hand, a resistance gene is introduced, the plant cells recognize the signal from the avirulence-gene-carrying bacterium and undergo the HR because the expressed resistance gene product complements the function (Fig. 9, top panel, left). In this case, the plant cells do not have enough time to accumulate a large amount of reporter gene product before their death. Given the transformation efficiency estimated by a proper control (such as the uninfected half of the leaf), measuring the accumulation of reporter gene product can thus indicate whether the gene to be assayed complements the resistance gene function.

In one working example, we now demonstrate the effectiveness of the transient expression assay, using the bacterial avirulence gene *avrRpt2* and the corresponding *Arabidopsis thaliana* resistance gene *RPS2* (Fig. 9, bottom panel). In brief, *rps2* mutant leaves, preinfected with *P. syringae* carrying *avrRpt2*, were co-bombarded with two plasmids, one of which contained the

RPS2 gene and the other the Escherichia coli *uidA* gene encoding β-glucuronidase (GUS; Jefferson et al., 1986, supra). Both the *RPS2* and *uidA* genes are located downstream of the strong constitutive *35S* promoter from cauliflower mosaic virus (Odell et al., infra). If the *35S-RPS2* construct complements the *rps2* mutation, the transformed cells rapidly undergo programmed cell death in response to the *P. syringae* carrying *avrRpt2*, and relatively little GUS activity accumulates. If the *rps2* mutation is not complemented, cell death does not occur and high levels of GUS activity accumulate. These differences in GUS activity are detected histochemically. Because the cDNA library used to identify *RPS2* was constructed in the expression vector pKEx4tr, the *35S-RPS2* cDNA construct in pKEx4tr could be used directly in the transient assay. As shown in Fig. 11, pKEx4tr is a cDNA expression vector designed for the unidirectional insertion of cDNA inserts. Inserted cDNA is expressed under the control of the 355 cauliflower mosaic virus promoter.

Our results are shown in Fig. 9, lower panel. In this experiment, we infected one side of a leaf of an *rps2* mutant plant with *P. syringae* pv. *phaseloicola* 3121 carrying *avrRpt2* (*Psp* 3121/*avrRpt2*). *Psp* 3121 is a weak pathogen of *A. thaliana* and *Psp 3121/avrRpt2* can elicit an HR in a plant carrying the resistance gene *RPS2* (e.g., a wild type plant). Leaves of 5-week-old *Arabidopsis* plants were infiltrated with an appropriate bacterial suspension at a dose of 2 x 10^8/ml by hand infiltration as described (Dong et al., supra). After an incubation period (typically 2-4 hours), the leaves were bombarded using a Bio-Rad PDS-1000/He apparatus (1100 psi) after 2-4 hr of infection. Gold particles were prepared according to the instructions of the manufacturer. For each bombardment, 1.4 μg of pKEx4tr-G, 0.1 μg of a

plasmid to be tested, and 0.5 mg of 1 μm gold particles were used. After the bombardment, the leaves were incubated in a humidity chamber at 22°C for 1 day and then subjected to a histochemical GUS staining using 5-bromo-4-chloro-3-indiyl glucuronidase (X-Gluc) at 37°C for 12 hr (Jefferson, 1987, supra). This staining method with X-gluc stains cells expressing GUS enzyme with a blue color. The uninfected side of the leaf serves as a control for transformation efficiency of the leaf because in a single leaf, transformation efficiency (i.e., density of transformed cells) is similar on both sides of the leaf. If transformed cells on the infected side are rapidly killed, staining of the cells on the infected side is weaker than staining on the uninfected side. When the resistance gene *RPS2* was co-introduced, the transformed cells on the infected side of the leaf showed much weaker staining than ones on the uninfected side (Fig. 10). In contrast, when an unrelated gene was co-introduced, the transformed cells on the infected side showed similar staining intensity to ones on the uninfected side (Fig. 10).

Thus, as summarized in the Table 2, *35S-RPS4* (cDNA 4), but not cDNA-5 or cDNA-6, complemented the HR phenotype of *rps2-101C*. (See Figure 1)

Table 2

Gene Tested	Response (Decreased GUSActivity)[a]
ΔGUS (*35S-uidA* containing internal *uidA* deletion)	-
cDNA-5 (*35S-AB11*)	
cDNA-4 (*35S-RPS2*)	+
cDNA-6 (*35S-CK1*)	

[a]When decreased GUS activity was observed on the infiltrated side of the leaf, the response was scored as plus (Fig. 10).

Both *RPS2* cDNA-4 clones 4 and 11, corresponding to the two RPS2 different transcript sizes, complemented the *rps2* mutant phenotype, indicating that both transcripts encode a functional product. Moreover, *35S-RPS2* also complemented mutants *rps2-102C*, *rps2-101N*, and *rps2-201C*, further confirming that the *rps2-101C*, *rps2-102C*, *rps2-201C* and *rps2-101N* mutations are all allelic. In short, the cloned *RPS2* gene complemented the *rps2* mutation in this transient expression assay, and complementation by *RPS2* was observed in all four available *rps2* mutant stains.

Next we used the transient assay system to test the specificity of the cloned *RPS2* gene for an *avrRpt2*-generated signal (i.e., the "gene-for-gene" specificity of a *P. syringae* avirulence gene and a corresponding *A. thaliana* resistance gene (*avrRpm1* and *RPM1*, respectively)). This experiment involved the use of an *rps2-101 rpm1* double mutant that cannot mount an HR when challenged with *P. syringae* carrying *avrRpt2* or the unrelated avirulence gene *avrRpm1* (Debener et al., Plant Journal 1:289-302, 1991). As summarized in Table 3, complementation of the *rps2* mutant phenotype by *35S-RPS2* was only observed in the presence of a signal generated by *avrRpt2*, indicating that *RPS2* does not simply sensitize the plant resistance response in a nonspecific manner.

Table 3

avr Gene	Construct Cobombarded with *35S-uidA*	Response[a]
None (vector only)	ΔGUS[b]	-
avrRPt2	ΔGUS	-
avrRpm1	ΔGUS	-
None (vector only)	*35S-RPS2*	-
avrRpt2	*35S-RPS2*	+
avrRpm1	*35S-RPS2*	-

[a]When decreased GUS activity was observed on the infiltrated side of the leaf, the response was scored as plus. (Figure 10, panel B)

[b]ΔGUS is *35S-uidA* containing an internal deletion in the *uidA* gene.

Also as shown in Table 3, the *RPS2* gene complemented the mutant phenotype when leaves were infected with *Psp* 3121/*avrRpt2* but not with *Psp* 3121/*avrRpm1*. Therefore, the *RPS2* gene complemented only the *rps2* mutation; it did not the *rpm1* mutation.

We have also discovered that overexpression of an rps gene family member, e.g., rps2 but not other genes, in the transient assay leads to apparent cell death, obviating the need to know the corresponding avirulence gene for a putative resistance gene that has been cloned.

Using this assay, any plant disease-resistance gene may be identified from a cDNA expression library. In one particular example, a cDNA library is constructed in an expression vector and then introduced as described herein into a plant cultivar or its corresponding mutant plant lacking the resistance gene of interest. Preferably, the cDNA library is divided into small pools, and each pool co-introduced with a reporter gene. If a pool contains a resistance gene clone (i.e., the pool

"complements" the resistance gene function), the positive pool is divided into smaller pools and the same procedure is repeated until identification of a single positive clone is ultimately achieved. This approach facilitates the cloning of any resistance gene of interest without genetic crosses or the creation of transgenics.

We now describe the cloning of another member of the RPS gene family, the Prf gene of tomato.

The initial step for the cloning of the Prf gene came from classical genetic analysis which showed that Prf was tightly linked to the tomato Pto gene (Salmeron et al., The Plant Cell 6:511-520, 1994). This prompted construction of a cosmid contig of 200 kb in length which encompassed the Pto locus. DNA probes from this contig were used to screen a tomato cDNA library constructed using tomato leaf tissue that had been infected with Pst expressing the avrPto avirulence gene as source material. Two classes of cDNAs were identified based on cross-hybridization of clones to each other. While one class corresponded to members of the Pto gene family, the other class displayed no hybridization to Pto family members. Taking the assumption (based on the aforementioned genetic analysis) that Prf might reside extremely close to the Pto gene, cDNAs from the second class were analyzed further as candidate Prf clones. These clones were hybridized to filters containing DNAs from six independent prf mutant lines that had been isolated by diepoxybutane or fast neutron treatment. In one of the fast neutron mutants, the cDNA probe revealed a 1.1 kb deletion in the genomic DNA, suggesting that the cDNA clone might in fact represent Prf. Wild-type DNA corresponding to the deletion was cloned from Prf/Prf tomato. A 5 kb region was sequenced and found to potentially encode a protein containing P-loop and leucine-rich repeat motifs, supporting the hypothesis

that this DNA encoded Prf. The corresponding DNA was cloned and sequenced from the fast neutron mutant plant. Sequencing this DNA confirmed the mutation to be a simple 1.1 kb deletion excising DNA between the potential P-loop and leucine-rich repeat coding regions. The gene is expressed based on RT-PCR analysis which has shown that an mRNA is transcribed from this region. The identity of the cloned DNA as the Prf gene is based on both the existence of the deletion mutation and the predicted protein sequence, which reveals patches of strong similarity to other cloned disease resistance gene products throughout the amino-terminal half (as described herein). A partial sequence of the Prf gene is shown in Figure 12.

RPS Expression in Transgenic Plant Cells and Plants

The expression of the *RPS2* genes in plants susceptible to pathogens carrying *avrRpt2* is achieved by introducing into a plant a DNA sequence containing the *RPS2* gene for expression of the Rps2 polypeptide. A number of vectors suitable for stable transfection of plant cells or for the establishment of transgenic plants are available to the public; such vectors are described in, e.g., Pouwels et al., *Cloning Vectors: A Laboratory Manual*, 1985, Supp. 1987); Weissbach and Weissbach, *Methods for Plant Molecular Biology*, Academic Press, 1989; and Gelvin et al., *Plant Molecular Biology Manual*, Kluwer Academic Publishers, 1990. Typically, plant expression vectors include (1) one or more cloned plant genes under the transcriptional control of 5′ and 3′ regulatory sequences and (2) a dominant selectable marker. Such plant expression vectors may also contain, if desired, a promoter regulatory region (e.g., a regulatory region controlling inducible or constitutive, environmentally- or developmentally-regulated, or cell-

or tissue-specific expression), a transcription initiation start site, a ribosome binding site, an RNA processing signal, a transcription termination site, and/or a polyadenylation signal.

An example of a useful plant promoter which could be used to express a plant resistance gene according to the invention is a caulimovirus promoter, e.g., the cauliflower mosaic virus (CaMV) 35S promoter. These promoters confer high levels of expression in most plant tissues, and the activity of these promoters is not dependent on virtually encoded proteins. CaMV is a source for both the 35S and 19S promoters. In most tissues of transgenic plants, the CaMV 35S promoter is a strong promoter (see, e.g., Odel et al., Nature 313:810, (1985)). The CaMV promoter is also highly active in monocots (see, e.g., Dekeyser et al., Plant Cell 2:591, (1990); Terada and Shimamoto, Mol. Gen. Genet. 220:389, (1990)).

Other useful plant promoters include, without limitation, the nonpaline synthase promoter (An et al., Plant Physiol. 88:547, (1988)) and the octopine synthase promoter (Fromm et al., Plant Cell 1:977, (1989)).

For certain applications, it may be desirable to produce the *RPS2* gene product or the *avrRpt2* gene product in an appropriate tissue, at an appropriate level, or at an appropriate developmental time. Thus, there are a variety of gene promoters, each with its own distinct characteristics embodied in its regulatory sequences, shown to be regulated in response to the environment, hormones, and/or developmental cues. These include gene promoters that are responsible for (1) heat-regulated gene expression (see, e.g., Callis et al., Plant Physiol. 88: 965, (1988)), (2) light-regulated gene expression (e.g., the pea *rbcS-3A* described by Kuhlemeier et al., Plant Cell 1: 471, (1989); the maize *rbcS* promoter

described by Schaffner and Sheen, Plant Cell 3: 997, (1991); or the chlorophyll a/b-binding protein gene found in pea described by Simpson et al., EMBO J. 4: 2723, (1985)), (3) hormone-regulated gene expression (e.g., the abscisic acid responsive sequences from the *Em* gene of wheat described Marcotte et al., Plant Cell 1:969, (1989)), (4) wound-induced gene expression (e.g., of *wunI* described by Siebertz et al., Plant Cell 1: 961, (1989)), or (5) organ-specific gene expression (e.g., of the tuber-specific storage protein gene described by Roshal et al., EMBO J. 6:1155, (1987); the 23-kDa zein gene from maize described by Schernthaner et al., EMBO J. 7: 1249, (1988); or the French bean ß-phaseolin gene described by Bustos et al., Plant Cell 1:839, (1989)).

Plant expression vectors may also optionally include RNA processing signals, e.g, introns, which have been shown to be important for efficient RNA synthesis and accumulation (Callis et al., Genes and Dev. 1: 1183, (1987)). The location of the RNA splice sequences can influence the level of transgene expression in plants. In view of this fact, an intron may be positioned upstream or downstream of an Rps2 polypeptide-encoding sequence in the transgene to modulate levels of gene expression.

In addition to the aforementioned 5′ regulatory control sequences, the expression vectors may also include regulatory control regions which are generally present in the 3′ regions of plant genes (Thornburg et al., Proc. Natl Acad. Sci USA 84: 744, (1987); An et al., Plant Cell 1: 115, (1989)). For example, the 3′ terminator region may be included in the expression vector to increase stability of the mRNA. One such terminator region may be derived from the PI-II terminator region of potato. In addition, other commonly

used terminators are derived from the octopine or nopaline synthase signals.

The plant expression vector also typically contains a dominant selectable marker gene used to identify the cells that have become transformed. Useful selectable marker genes for plant systems include genes encoding antibiotic resistance genes, for example, those encoding resistance to hygromycin, kanamycin, bleomycin, G418, streptomycin or spectinomycin. Genes required for photosynthesis may also be used as selectable markers in photosynthetic-deficient strains. Finally, genes encoding herbicide resistance may be used as selectable markers; useful herbicide resistance genes include the *bar* gene encoding the enzyme phosphinothricin acetyltransferase, which confers resistance to the broad spectrum herbicide Basta® (Hoechst AG, Frankfurt, Germany).

Efficient use of selectable markers is facilitated by a determination of the susceptibility of a plant cell to a particular selectable agent and a determination of the concentration of this agent which effectively kills most, if not all, of the transformed cells. Some useful concentrations of antibiotics for tobacco transformation include, e.g., 75-100 μg/ml (kanamycin), 20-50 μg/ml (hygromycin), or 5-10 μg/ml (bleomycin). A useful strategy for selection of transformants for herbicide resistance is described, e.g., in Vasil I.K., *Cell Culture and Somatic Cell Genetics of Plants*, Vol I, II, III Laboratory Procedures and Their Applications Academic Press, New York, 1984.

It should be readily apparent to one skilled in the field of plant molecular biology that the level of gene expression is dependent not only on the combination of promoters, RNA processing signals and terminator

elements, but also on how these elements are used to increase the levels of gene expression.

The above exemplary techniques may be used for the expression of any gene in the RPS family.

Plant Transformation

Upon construction of the plant expression vector, several standard methods are known for introduction of the recombinant genetic material into the host plant for the generation of a transgenic plant. These methods include (1) Agrobacterium-mediated transformation (*A. tumefaciens* or *A. rhizogenes*) (see, e.g., Lichtenstein and Fuller In: *Genetic Engineering*, vol 6, PWJ Rigby, ed, London, Academic Press, 1987; and Lichtenstein, C.P., and Draper, J,. In: *DNA Cloning*, Vol II, D.M. Glover, ed, Oxford, IRI Press, 1985), (2) the particle delivery system (see, e.g., Gordon-Kamm et al., Plant Cell 2:603, (1990); or BioRad Technical Bulletin 1687, *supra*), (3) microinjection protocols (see, e.g., Green et al., *Plant Tissue and Cell Culture*, Academic Press, New York, 1987), (4) polyethylene glycol (PEG) procedures (see, e.g., Draper et al., Plant Cell Physiol 23:451, (1982); or e.g., Zhang and Wu, Theor. Appl. Genet. 76:835, (1988)), (5) liposome-mediated DNA uptake (see, e.g., Freeman et al., Plant Cell Physiol 25: 1353, (1984)), (6) electroporation protocols (see, e.g., Gelvin et al supra; Dekeyser et al. supra; or Fromm et al Nature 319: 791, (1986)), and (7) the vortexing method (see, e.g., Kindle, K., Proc. Natl. Acad. Sci., USA 87:1228, (1990)).

The following is an example outlining an *Agrobacterium*-mediated plant transformation. The general process for manipulating genes to be transferred into the genome of plant cells is carried out in two phases. First, all the cloning and DNA modification steps are done in *E. coli*, and the plasmid containing the gene

construct of interest is transferred by conjugation into *Agrobacterium*. Second, the resulting *Agrobacterium* strain is used to transform plant cells. Thus, for the generalized plant expression vector, the plasmid contains an origin of replication that allows it to replicate in *Agrobacterium* and a high copy number origin of replication functional in *E. coli*. This permits facile production and testing of transgenes in *E.coli* prior to transfer to *Agrobacterium* for subsequent introduction into plants. Resistance genes can be carried on the vector, one for selection in bacteria, e.g., streptomycin, and the other that will express in plants, e.g., a gene encoding for kanamycin resistance or an herbicide resistance gene. Also present are restriction endonuclease sites for the addition of one or more transgenes operably linked to appropriate regulatory sequences and directional T-DNA border sequences which, when recognized by the transfer functions of *Agrobacterium*, delimit the region that will be transferred to the plant.

In another example, plant cells may be transformed by shooting into the cell tungsten microprojectiles on which cloned DNA is precipitated. In the Biolistic Apparatus (Bio-Rad, Hercules, CA) used for the shooting, a gunpowder charge (22 caliber Power Piston Tool Charge) or an air-driven blast drives a plastic macroprojectile through a gun barrel. An aliquot of a suspension of tungsten particles on which DNA has been precipitated is placed on the front of the plastic macroprojectile. The latter is fired at an acrylic stopping plate that has a hole through it that is too small for the macroprojectile to go through. As a result, the plastic macroprojectile smashes against the stopping plate and the tungsten microprojectiles continue toward their target through the hole in the plate. For the instant invention the target

can be any plant cell, tissue, seed, or embryo. The DNA introduced into the cell on the microprojectiles becomes integrated into either the nucleus or the chloroplast.

Transfer and expression of transgenes in plant cells is now routine practice to those skilled in the art. It has become a major tool to carry out gene expression studies and to attempt to obtain improved plant varieties of agricultural or commercial interest.

Transgenic Plant Regeneration

Plant cells transformed with a plant expression vector can be regenerated, e.g., from single cells, callus tissue or leaf discs according to standard plant tissue culture techniques. It is well known in the art that various cells, tissues and organs from almost any plant can be successfully cultured to regenerate an entire plant; such techniques are described, e.g., in Vasil supra; Green et al., supra; Weissbach and Weissbach, supra; and Gelvin et al., supra.

In one possible example, a vector carrying a selectable marker gene (e.g., kanamycin resistance), a cloned *RPS2* gene under the control of its own promoter and terminator or, if desired, under the control of exogenous regulatory sequences such as the 35S CaMV promoter and the nopaline synthase terminator is transformed into *Agrobacterium*. Transformation of leaf tissue with vector-containing *Agrobacterium* is carried out as described by Horsch et al. (Science 227: 1229, (1985)). Putative transformants are selected after a few weeks (e.g., 3 to 5 weeks) on plant tissue culture media containing kanamycin (e.g. 100 μg/ml). Kanamycin-resistant shoots are then placed on plant tissue culture media without hormones for root initiation. Kanamycin-resistant plants are then selected for greenhouse growth.

If desired, seeds from self-fertilized transgenic plants can then be sowed in a soil-less media and grown in a greenhouse. Kanamycin-resistant progeny are selected by sowing surfaced sterilized seeds on hormone-free kanamycin-containing media. Analysis for the integration of the transgene is accomplished by standard techniques (see, e.g., Ausubel et al. supra; Gelvin et al. supra).

Transgenic plants expressing the selectable marker are then screened for transmission of the transgene DNA by standard immunoblot and DNA and RNA detection techniques. Each positive transgenic plant and its transgenic progeny are unique in comparison to other transgenic plants established with the same transgene. Integration of the transgene DNA into the plant genomic DNA is in most cases random and the site of integration can profoundly effect the levels, and the tissue and developmental patterns of transgene expression. Consequently, a number of transgenic lines are usually screened for each transgene to identify and select plants with the most appropriate expression profiles.

Transgenic lines are evaluated for levels of transgene expression. Expression at the RNA level is determined initially to identify and quantitate expression-positive plants. Standard techniques for RNA analysis are employed and include PCR amplification assays using oligonucleotide primers designed to amplify only transgene RNA templates and solution hybridization assays using transgene-specific probes (see, e.g., Ausubel et al., supra). The RNA-positive plants are then analyzed for protein expression by Western immunoblot analysis using Rps2 polypeptide-specific antibodies (see, e.g., Ausubel et al., supra). In addition, *in situ* hybridization and immunocytochemistry according to standard protocols can be done using transgene-specific

nucleotide probes and antibodies, respectively, to localize sites of expression within transgenic tissue.

Once the Rps2 polypeptide has been expressed in any cell or in a transgenic plant (e.g., as described above), it can be isolated using any standard technique, e.g., affinity chromatography. In one example, an anti-Rps2 antibody (e.g., produced as described in Ausubel et al., supra, or by any standard technique) may be attached to a column and used to isolate the polypeptide. Lysis and fractionation of Rps2-producing cells prior to affinity chromatography may be performed by standard methods (see, e.g., Ausubel et al., supra). Once isolated, the recombinant polypeptide can, if desired, be further purified, e.g., by high performance liquid chromatography (see, e.g., Fisher, *Laboratory Techniques In Biochemistry And Molecular Biology*, Work and Burdon, eds., Elsevier, 1980).

These general techniques of polypeptide expression and purification can also be used to produce and isolate useful Rps2 fragments or analogs.

Antibody Production

Using a polypeptide described above (e.g., the recombinant protein or a chemically synthesized *RPS* peptide based on its deduced amino acid sequence), polyclonal antibodies which bind specifically to an *RPS* polypeptide may be produced by standard techniques (see, e.g., Ausubel et al., supra) and isolated, e.g., following peptide antigen affinity chromatography. Monoclonal antibodies can also be prepared using standard hybridoma technology (see, e.g., Kohler et al., *Nature* 256: 495, 1975; Kohler et al., *Eur. J. Immunol.* 6: 292, 1976; Hammerling et al., in *Monoclonal Antibodies and T Cell Hybridomas*, Elsevier, N.Y., 1981; and Ausubel et al., supra).

Once produced, polyclonal or monoclonal antibodies are tested for specific *RSP* polypeptide recognition by Western blot or immunoprecipitation analysis (by methods described in Ausubel et al., supra). Antibodies which specifically recognize a *RPS* polypeptide are considered to be useful in the invention; such antibodies may be used, e.g., for screening recombinant expression libraries as described in Ausubel et al., supra. Exemplary peptides (derived from Rps2) for antibody production include:

LKFSYDNLESDLL [SEQ ID NO: 188]

GVYGPGGVGKTTLMQS [SEQ ID NO: 189]

GGLPLALITLGGAM [SEQ ID NO: 190]

Use

Introduction of *RPS2* into a transformed plant cell provides for resistance to bacterial pathogens carrying the *avrRpt2* avirulence gene. For example, transgenic plants of the instant invention expressing *RPS2* might be used to alter, simply and inexpensively, the disease resistance of plants normally susceptible to plant pathogens carrying the avirulence gene, *avrRpt2*.

The invention also provides for broad-spectrum pathogen resistance by mimicking the natural mechanism of host resistance. First, the *RPS2* transgene is expressed in plant cells at a sufficiently high level to initiate the plant defense response constitutively in the absence of signals from the pathogen. The level of expression associated with plant defense response initiation is determined by measuring the levels of defense response gene expression as described in Dong et al., supra. Second, the *RPS2* transgene is expressed by a controllable promoter such as a tissue-specific promoter, cell-type specific promoter or by a promoter that is induced by an external signal or agent thus limiting the temporal and

tissue expression of a defense response. Finally, the *RPS2* gene product is co-expressed with the *avrRpt2* gene product. The *RPS2* gene is expressed by its natural promoter, by a constitutively expressed promoter such as the CaMV 35S promoter, by a tissue-specific or cell-type specific promoter, or by a promoter that is activated by an external signal or agent. Co-expression of *RPS2* and *avrRpt2* will mimic the production of gene products associated with the initiation of the plant defense response and provide resistance to pathogens in the absence of specific resistance gene-avirulence gene corresponding pairs in the host plant and pathogen.

The invention also provides for expression in plant cells of a nucleic acid having the sequence of Fig. 2 or the expression of a degenerate variant thereof encoding the amino acid sequence of open reading frame "a" of Fig. 2.

The invention further provides for the isolation of nucleic acid sequences having about 50% or greater sequence identity to *RPS2* by using the *RPS2* sequence of Fig. 2 or a portion thereof greater than 9 nucleic acids in length, and preferably greater than about 18 nucleic acids in length as a probe. Appropriate reduced hybridization stringency conditions are utilized to isolate DNA sequences having about 50% or greater sequence identity to the *RPS2* sequence of Fig. 2.

Also provided by the invention are short conserved regions characteristic of *RPS* disease resistance genes. These conserved regions provide oligonucleotide sequences useful for the production of hybridization probes and PCR primers for the isolation of other plant disease-resistance genes.

Both the RPS2 gene and related RPS family genes provide disease resistance to plants, especially crop plants, most especially important crop plants such as

tomato, pepper, maize, wheat, rice and legumes such as soybean and bean, or any plant which is susceptible to pathogens carrying an avirulence gene, e.g., the *avrRpt2* avirulence gene. Such pathogens include, but are not limited to, *Pseudomonas syringae* strains.

The invention also includes any biologically active fragment or analog of an Rps2 polypeptide. By "biologically active" is meant possessing any <u>in vivo</u> activity which is characteristic of the Rps2 polypeptide shown in Fig. 2. A useful Rps2 fragment or Rps2 analog is one which exhibits a biological activity in any biological assay for disease resistance gene product activity, for example, those assays described by Dong et al. (1991), <u>supra</u>; Yu et al. (1993) <u>supra</u>; Kunkel et al. (1993) <u>supra</u>; and Whalen et al. (1991). In particular, a biologically active Rps2 polypeptide fragment or analog is capable of providing substantial resistance to plant pathogens carrying the *avrRpt2* avirulence gene. By substantial resistance is meant at least partial reduction in susceptibility to plant pathogens carrying the *avrRpt2* gene.

Preferred analogs include Rps2 polypeptides (or biologically active fragments thereof) whose sequences differ from the wild-type sequence only by conservative amino acid substitutions, for example, substitution of one amino acid for another with similar characteristics (e.g., valine for glycine, arginine for lysine, etc.) or by one or more non-conservative amino acid substitutions, deletions, or insertions which do not abolish the polypeptide's biological activity.

Analogs can differ from naturally occurring Rps2 polypeptide in amino acid sequence or can be modified in ways that do not involve sequence, or both. Analogs of the invention will generally exhibit at least 70%, preferably 80%, more preferably 90%, and most preferably

95% or even 99%, homology with a segment of 20 amino acid residues, preferably 40 amino acid residues, or more preferably the entire sequence of a naturally occurring Rps2 polypeptide sequence.

Alterations in primary sequence include genetic variants, both natural and induced. Also included are analogs that include residues other than naturally occurring L-amino acids, e.g., D-amino acids or non-naturally occurring or synthetic amino acids, e.g., β or γ amino acids. Also included in the invention are Rps2 polypeptides modified by *in vivo* chemical derivatization of polypeptides, including acetylation, methylation, phosphorylation, carboxylation, or glycosylation.

In addition to substantially full-length polypeptides, the invention also includes biologically active fragments of the polypeptides. As used herein, the term "fragment", as applied to a polypeptide, will ordinarily be at least 20 residues, more typically at least 40 residues, and preferably at least 60 residues in length. Fragments of Rps2 polypeptide can be generated by methods known to those skilled in the art. The ability of a candidate fragment to exhibit a biological activity of Rps2 can be assessed by those methods described herein. Also included in the invention are Rps2 polypeptides containing residues that are not required for biological activity of the peptide, e.g., those added by alternative mRNA splicing or alternative protein processing events.

Other embodiments are within the following claims.

SEQUENCE LISTING

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2903 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

AAGTAAAAGA AAGAGCGAGA AATCATCGAA ATGGATTTCA TCTCATCTCT TATCGTTGGC 60

TGTGCTCAGG TGTTGTGTGA ATCTATGAAT ATGGCGGAGA GAAGAGGACA TAAGACTGAT 120

CTTAGACAAG CCATCACTGA TCTTGAAACA GCCATCGGTG ACTTGAAGGC CATACGTGAT 180

GACCTGACTT TACGGATCCA ACAAGACGGT CTAGAGGGAC GAAGCTGCTC AAATCGTGCC 240

AGAGAGTGGC TTAGTGCGGT GCAAGTAACG GAGACTAAAA CAGCCCTACT TTTAGTGAGG 300

TTTAGGCGTC GGGAACAGAG GACGCGAATG AGGAGGAGAT ACCTCAGTTG TTTCGGTTGT 360

GCCGACTACA AACTGTGCAA GAAGGTTTCT GCCATATTGA AGAGCATTGG TGAGCTGAGA 420

GAACGCTCTG AAGCTATCAA AACAGATGGC GGGTCAATTC AAGTAACTTG TAGAGAGATA 480

CCCATCAAGT CCGTTGTCGG AAATACCACG ATGATGGAAC AGGTTTTGGA ATTTCTCAGT 540

GAAGAAGAAG AAAGAGGAAT CATTGGTGTT TATGGACCTG GTGGGGTTGG GAAGACAACG 600

TTAATGCAGA GCATTAACAA CGAGCTGATC ACAAAAGGAC ATCAGTATGA TGTACTGATT 660

TGGGTTCAAA TGTCCAGAGA ATTCGGCGAG TGTACAATTC AGCAAGCCGT TGGAGCACGG 720

TTGGGTTTAT CTTGGGACGA GAAGGAGACC GGCGAAAACA GAGCTTTGAA GATATACAGA 780

GCTTTGAGAC AGAAACGTTT CTTGTTGTTG CTAGATGATG TCTGGGAAGA GATAGACTTG 840

GAGAAAACTG GAGTTCCTCG ACCTGACAGG GAAAACAAAT GCAAGGTGAT GTTCACGACA 900

CGGTCTATAG CATTATGCAA CAATATGGGT GCGGAATACA AGTTGAGAGT GGAGTTTCTG 960

GAGAAGAAAC ACGCGTGGGA GCTGTTCTGT AGTAAGGTAT GGAGAAAAGA TCTTTTAGAG 1020

TCATCATCAA TTCGCCGGCT CGCGGAGATT ATAGTGAGTA AATGTGGAGG ATTGCCACTA 1080

GCGTTGATCA CTTTAGGAGG AGCCATGGCT CATAGAGAGA CAGAAGAAGA GTGGATCCAT 1140

GCTAGTGAAG TTCTGACTAG ATTTCCAGCA GAGATGAAGG GTATGAACTA TGTATTTGCC 1200

CTTTTGAAAT TCAGCTACGA CAACCTCGAG AGTGATCTGC TTCGGTCTTG TTTCTTGTAC 1260

TGCGCTTTAT TCCCAGAAGA ACATTCTATA GAGATCGAGC AGCTTGTTGA GTACTGGGTC 1320

GGCGAAGGGT TTCTCACCAG CTCCCATGGC GTTAACACCA TTTACAAGGG ATATTTTCTC 1380

ATTGGGGATC TGAAAGCGGC ATGTTTGTTG GAAACCGGAG ATGAGAAAAC ACAGGTGAAG 1440

ATGCATAATG TGGTCAGAAG CTTTGCATTG TGGATGGCAT CTGAACAGGG GACTTATAAG 1500

GAGCTGATCC TAGTTGAGCC TAGCATGGGA CATACTGAAG CTCCTAAAGC AGAAAACTGG 1560

CGACAAGCGT TGGTGATCTC ATTGTTAGAT AACAGAATCC AGACCTTGCC TGAAAAACTC 1620

ATATGCCCGA AACTGACAAC ACTGATGCTC CAACAGAACA GCTCTTTGAA GAAGATTCCA 1680

ACAGGGTTTT TCATGCATAT GCCTGTTCTC AGAGTCTTGG ACTTGTCGTT CACAAGTATC 1740

ACTGAGATTC CGTTGTCTAT CAAGTATTTG GTGGAGTTGT ATCATCTGTC TATGTCAGGA 1800

ACAAAGATAA GTGTATTGCC ACAGGAGCTT GGGAATCTTA GAAAACTGAA GCATCTGGAC 1860

CTACAAAGAA CTCAGTTTCT TCAGACGATC CCACGAGATG CCATATGTTG GCTGAGCAAG 1920

CTCGAGGTTC TGAACTTGTA CTACAGTTAC GCCGGTTGGG AACTGCAGAG CTTTGGAGAA 1980

GATGAAGCAG AAGAACTCGG ATTCGCTGAC TTGGAATACT TGGAAAACCT AACCACACTC 2040

GGTATCACTG TTCTCTCATT GGAGACCCTA AAAACTCTCT TCGAGTTCGG TGCTTTGCAT 2100

AAACATATAC AGCATCTCCA CGTTGAAGAG TGCAATGAAC TCCTCTACTT CAATCTCCCA 2160

TCACTCACTA ACCATGGCAG GAACCTGAGA AGACTTAGCA TTAAAAGTTG CCATGACTTG 2220

GAGTACCTGG TCACACCCGC AGATTTTGAA AATGATTGGC TTCCGAGTCT AGAGGTTCTG 2280

ACGTTACACA GCCTTCACAA CTTAACCAGA GTGTGGGGAA ATTCTGTAAG CCAAGATTGT 2340

CTGCGGAATA TCCGTTGCAT AAACATTTCA CACTGCAACA AGCTGAAGAA TGTCTCATGG 2400

GTTCAGAAAC TCCCAAAGCT AGAGGTGATT GAACTGTTCG ACTGCAGAGA GATAGAGGAA 2460

TTGATAAGCG AACACGAGAG TCCATCCGTC GAAGATCCAA CATTGTTCCC AAGCCTGAAG 2520

ACCTTGAGAA CTAGGGATCT GCCAGAACTA AACAGCATCC TCCCATCTCG ATTTTCATTC 2580

CAAAAAGTTG AAACATTAGT CATCACAAAT TGCCCCAGAG TTAAGAAACT GCCGTTTCAG 2640

GAGAGGAGGA CCCAGATGAA CTTGCCAACA GTTTATTGTG AGGAGAAATG GTGGAAAGCA 2700

CTGGAAAAAG ATCAACCAAA CGAAGAGCTT TGTTATTTAC CGCGCTTTGT TCCAAATTGA 2760

TATAAGAGCT AAGAGCACTC TGTACAAATA TGTCCATTCA TAAGTAGCAG GAAGCCAGGA 2820

AGGTTGTTCC AGTGAAGTCA TCAACTTTCC ACATAGCCAC AAAACTAGAG ATTATGTAAT 2880

CATAAAAACC AAACTATCCG CGA 2903

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 885 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Lys Lys Glu Arg Glu Ile Ile Glu Met Asp Phe Ile Ser Ser Leu Ile
1 5 10 15

Val Gly Cys Ala Gln Val Leu Cys Glu Ser Met Asn Met Ala Glu Arg
20 25 30

Arg Gly His Lys Thr Asp Leu Arg Gln Ala Ile Thr Asp Leu Arg Ile
35 40 45

Gln Gln Asp Gly Leu Glu Gly Arg Ser Cys Ser Asn Arg Ala Arg Glu
50 55 60

Trp Leu Ser Ala Val Gln Val Thr Glu Thr Lys Thr Ala Leu Leu Leu
65 70 75 80

Val Arg Phe Arg Arg Arg Glu Gln Arg Thr Arg Met Arg Arg Arg Tyr
85 90 95

Leu Ser Cys Phe Gly Cys Ala Asp Tyr Lys Leu Cys Lys Lys Val Ser
100 105 110

Ala Ile Leu Lys Ser Ile Gly Glu Leu Arg Glu Arg Ser Glu Ala Ile
115 120 125

Lys Thr Asp Gly Gly Ser Ile Gln Val Thr Cys Arg Glu Ile Pro Ile
130 135 140

Lys Ser Val Val Gly Asn Thr Thr Met Met Glu Gln Val Leu Glu Phe
145 150 155 160

Leu Ser Glu Glu Glu Glu Arg Gly Ile Ile Gly Val Tyr Gly Pro Gly
165 170 175

Gly Val Gly Lys Thr Thr Leu Met Gln Ser Ile Asn Asn Glu Leu Ile
180 185 190

Thr Lys Gly His Gln Tyr Asp Val Leu Ile Trp Val Gln Met Ser Arg
195 200 205

Glu Phe Gly Glu Cys Thr Ile Gln Gln Ala Val Gly Ala Arg Leu Gly
210 215 220

Leu Ser Trp Asp Glu Lys Glu Thr Gly Glu Asn Arg Ala Leu Lys Ile
225 230 235 240

Tyr Arg Ala Leu Arg Gln Lys Arg Phe Leu Leu Leu Leu Asp Asp Val
245 250 255

Trp Glu Glu Ile Asp Leu Glu Lys Thr Gly Val Pro Arg Pro Asp Arg
260 265 270

Glu Asn Lys Cys Lys Val Met Phe Thr Thr Arg Ser Ile Ala Leu Cys
275 280 285

Asn Asn Met Gly Ala Glu Tyr Lys Leu Arg Val Glu Phe Leu Glu Lys
290 295 300

Lys His Ala Trp Glu Leu Phe Cys Ser Lys Val Trp Arg Lys Asp Leu
305 310 315 320

Leu Glu Ser Ser Ser Ile Arg Arg Leu Ala Glu Ile Ile Val Ser Lys
325 330 335

Cys Gly Gly Leu Pro Leu Ala Leu Ile Thr Leu Gly Gly Ala Met Ala
340 345 350

His Arg Glu Thr Glu Glu Glu Trp Ile His Ala Ser Glu Val Leu Thr
355 360 365

Arg Phe Pro Ala Glu Met Lys Gly Met Asn Tyr Val Phe Ala Leu Leu
370 375 380

Lys Phe Ser Tyr Asp Asn Leu Glu Ser Asp Leu Leu Arg Ser Cys Phe
385 390 395 400

Leu Tyr Cys Ala Leu Phe Pro Glu Glu His Ser Ile Glu Ile Glu Gln
405 410 415

Leu Val Glu Tyr Trp Val Gly Glu Gly Phe Leu Thr Ser Ser His Gly
420 425 430

Val Asn Thr Ile Tyr Lys Gly Tyr Phe Leu Ile Gly Asp Leu Lys Ala
435 440 445

Ala Cys Leu Leu Glu Thr Gly Asp Glu Lys Thr Gln Val Lys Met His
450 455 460

Asn Val Val Arg Ser Phe Ala Leu Trp Met Ala Ser Glu Gln Gly Thr
465 470 475 480

Tyr Lys Glu Leu Ile Leu Val Glu Pro Ser Met Gly His Thr Glu Ala
485 490 495

Pro Lys Ala Glu Asn Trp Arg Gln Ala Leu Val Ile Ser Leu Leu Asp
500 505 510

Asn Arg Ile Gln Thr Leu Pro Glu Lys Leu Ile Cys Pro Lys Leu Thr
515 520 525

Thr Leu Met Leu Gln Gln Asn Ser Ser Leu Lys Lys Ile Pro Thr Gly
530 535 540

Phe Phe Met His Met Pro Val Leu Arg Val Leu Asp Leu Ser Phe Thr
545 550 555 560

Ser Ile Thr Glu Ile Pro Leu Ser Ile Lys Tyr Leu Val Glu Leu Tyr
565 570 575

His Leu Ser Met Ser Gly Thr Lys Ile Ser Val Leu Pro Gln Glu Leu
580 585 590

Gly Asn Leu Arg Lys Leu Lys His Leu Asp Leu Gln Arg Thr Gln Phe
595 600 605

Leu Gln Thr Ile Pro Arg Asp Ala Ile Cys Trp Leu Ser Lys Leu Glu
610 615 620

Val Leu Asn Leu Tyr Tyr Ser Tyr Ala Gly Trp Glu Leu Gln Ser Phe
625 630 635 640

Gly Glu Asp Glu Ala Glu Glu Leu Gly Phe Ala Asp Leu Glu Tyr Leu
645 650 655

Glu Asn Leu Thr Thr Leu Gly Ile Thr Val Leu Ser Leu Glu Thr Leu
660 665 670

Lys Thr Leu Phe Glu Phe Gly Ala Leu His Lys His Ile Gln His Leu
675 680 685

His Val Glu Glu Cys Asn Glu Leu Leu Tyr Phe Asn Leu Pro Ser Leu
690 695 700

Thr Asn His Gly Arg Asn Leu Arg Arg Leu Ser Ile Lys Ser Cys His
705 710 715 720

Asp Leu Glu Tyr Leu Val Thr Pro Ala Asp Phe Glu Asn Asp Trp Leu
725 730 735

Pro Ser Leu Glu Val Leu Thr Leu His Ser Leu His Asn Leu Arg Cys
740 745 750

Ile Asn Ile Ser His Cys Asn Lys Leu Lys Asn Val Ser Trp Val Gln
755 760 765

```
Lys Leu Pro Lys Leu Glu Val Ile Glu Leu Phe Asp Cys Arg Glu Ile
    770                 775                 780

Glu Glu Leu Ile Ser Glu His Glu Ser Pro Ser Val Glu Asp Pro Thr
785                 790                 795                 800

Leu Phe Pro Ser Leu Lys Thr Leu Arg Thr Arg Asp Leu Pro Glu Leu
                805                 810                 815

Asn Ser Ile Leu Pro Ser Arg Phe Ser Phe Gln Lys Val Glu Thr Leu
            820                 825                 830

Val Ile Thr Asn Cys Pro Arg Val Lys Lys Leu Pro Phe Gln Glu Arg
        835                 840                 845

Arg Thr Gln Met Asn Leu Pro Thr Val Tyr Cys Glu Glu Lys Trp Trp
    850                 855                 860

Lys Ala Leu Glu Lys Asp Gln Pro Asn Glu Glu Leu Cys Tyr Leu Pro
865                 870                 875                 880

Arg Phe Val Pro Asn
                885
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
Glu His Ser Val Gln Ile Cys Pro Phe Ile Ser Ser Arg Lys Pro Gly
1               5                   10                  15

Arg Leu Phe Gln
            20
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Ser His Gln Leu Ser Thr
1               5
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Arg Leu Cys Asn His Lys Asn Gln Thr Ile Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Ser Lys Arg Lys Ser Glu Lys Ser Ser Lys Trp Ile Ser Ser His Leu
1 5 10 15

Leu Ser Leu Ala Val Leu Arg Cys Cys Val Asn Leu
20 25

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Ile Trp Arg Arg Glu Glu Asp Ile Arg Leu Ile Leu Asp Lys Pro Ser
1 5 10 15

Leu Ile Leu Lys Gln Pro Ser Val Thr
20 25

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Arg Pro Tyr Val Met Thr
1 5

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Leu Tyr Gly Ser Asn Lys Thr Val
1 5

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Arg Asp Glu Ala Ala Gln Ile Val Pro Glu Ser Gly Leu Val Arg Cys
1 5 10 15

Lys

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Arg Arg Leu Lys Gln Pro Tyr Phe
1 5

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Gly Leu Gly Val Gly Asn Arg Gly Arg Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Gly Gly Asp Thr Ser Val Val Ser Val Val Pro Thr Thr Asn Cys Ala
1 5 10 15

Arg Arg Phe Leu Pro Tyr
20

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Arg Ala Leu Val Ser

1 5

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Glu Asn Ala Leu Lys Leu Ser Lys Gln Met Ala Gly Gln Phe Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Leu Val Glu Arg Tyr Pro Ser Ser Pro Leu Ser Glu Ile Pro Arg
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Trp Asn Arg Phe Trp Asn Phe Ser Val Lys Lys Lys Lys Glu Glu Ser
1 5 10 15

Leu Val Phe Met Asp Leu Val Gly Leu Gly Arg Gln Arg
20 25

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Cys Arg Ala Leu Thr Thr Ser
1 5

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Ser Gln Lys Asp Ile Ser Met Met Tyr
1 5

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Phe Gly Phe Lys Cys Pro Glu Asn Ser Ala Ser Val Gln Phe Ser Lys
1 5 10 15

Pro Leu Glu His Gly Trp Val Tyr Leu Gly Thr Arg Arg Arg Pro Ala
20 25 30

Lys Thr Glu Leu
35

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Arg Tyr Thr Glu Leu
1 5

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Asp Arg Asn Val Ser Cys Cys Cys
1 5

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Met Met Ser Gly Lys Arg
1 5

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Thr Trp Arg Lys Leu Glu Phe Leu Asp Leu Thr Gly Lys Thr Asn Ala
1 5 10 15

Arg

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Cys Ser Arg His Gly Leu
1 5

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

His Tyr Ala Thr Ile Trp Val Arg Asn Thr Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Glu Trp Ser Phe Trp Arg Arg Asn Thr Arg Gly Ser Cys Ser Val Val
1 5 10 15

Arg Tyr Gly Glu Lys Ile Phe
20

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Ser His His Gln Phe Ala Gly Ser Arg Arg Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Val Asn Val Glu Asp Cys His
1 5

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Glu Glu Pro Trp Leu Ile Glu Arg Gln Lys Lys Ser Gly Ser Met Leu
1 5 10 15

Val Lys Phe

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Leu Asp Phe Gln Gln Arg
1 5

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Thr Met Tyr Leu Pro Phe
1 5

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Asn Ser Ala Thr Thr Thr Ser Arg Val Ile Cys Phe Gly Leu Val Ser
1 5 10 15

Cys Thr Ala Leu Tyr Ser Gln Lys Asn Ile Leu
20 25

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Arg Ser Ser Ser Leu Leu Ser Thr Gly Ser Ala Lys Gly Phe Ser Pro

1 5 10 15

Ala Pro Met Ala Leu Thr Pro Phe Thr Arg Asp Ile Phe Ser Leu Gly
20 25 30

Ile

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Lys Arg His Val Cys Trp Lys Pro Glu Met Arg Lys His Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Arg Cys Ile Met Trp Ser Glu Ala Leu His Cys Gly Trp His Leu Asn
1 5 10 15

Arg Gly Leu Ile Arg Ser
20

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Leu Ser Leu Ala Trp Asp Ile Leu Lys Leu Leu Lys Gln Lys Thr Gly
1 5 10 15

Asp Lys Arg Trp
20

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Ile Thr Glu Ser Arg Pro Cys Leu Lys Asn Ser Tyr Ala Arg Asn
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Cys Ser Asn Arg Thr Ala Leu
1 5

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Arg Arg Phe Gln Gln Gly Phe Ser Cys Ile Cys Leu Phe Ser Glu Ser
1 5 10 15

Trp Thr Cys Arg Ser Gln Val Ser Leu Arg Phe Arg Cys Leu Ser Ser
20 25 30

Ile Trp Trp Ser Cys Ile Ile Cys Leu Cys Gln Glu Gln Arg
35 40 45

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Val Tyr Cys His Arg Ser Leu Gly Ile Leu Glu Asn
1 5 10

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Ser Ile Trp Thr Tyr Lys Glu Leu Ser Phe Phe Arg Arg Ser His Glu
1 5 10 15

Met Pro Tyr Val Gly
20

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Ala Ser Ser Arg Phe
1 5

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Thr Cys Thr Thr Val Thr Pro Val Gly Asn Cys Arg Ala Leu Glu Lys
1 5 10 15

Met Lys Gln Lys Asn Ser Asp Ser Leu Thr Trp Asn Thr Trp Lys Thr
20 25 30

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Pro His Ser Val Ser Leu Phe Ser His Trp Arg Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

Lys Leu Ser Ser Ser Ser Val Leu Cys Ile Asn Ile Tyr Ser Ile Ser
1 5 10 15

Thr Leu Lys Ser Ala Met Asn Ser Ser Thr Ser Ile Ser His His Ser
20 25 30

Leu Thr Met Ala Gly Thr
35

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Glu Asp Leu Ala Leu Lys Val Ala Met Thr Trp Ser Thr Trp Ser His
1 5 10 15

Pro Gln Ile Leu Lys Met Ile Gly Phe Arg Val
20 25

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Arg Tyr Thr Ala Phe Thr Thr
1 5

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

Pro Glu Cys Gly Glu Ile Leu
1 5

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Ala Lys Ile Val Cys Gly Ile Ser Val Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Thr Phe His Thr Ala Thr Ser
1 5

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Phe Arg Asn Ser Gln Ser
1 5

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Leu Asn Cys Ser Thr Ala Glu Arg
1 5

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Ala Asn Thr Arg Val His Pro Ser Lys Ile Gln His Cys Ser Gln Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Glu Leu Gly Ile Cys Gln Asn
1 5

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Thr Ala Ser Ser His Leu Asp Phe His Ser Lys Lys Leu Lys His
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Ser Ser Gln Ile Ala Pro Glu Leu Arg Asn Cys Arg Phe Arg Arg Gly
1 5 10 15

Gly Pro Arg

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Thr Cys Gln Gln Phe Ile Val Arg Arg Asn Gly Gly Lys His Trp Lys
1 5 10 15

Lys Ile Asn Gln Thr Lys Ser Phe Val Ile Tyr Arg Ala Leu Phe Gln
20 25 30

Ile Asp Ile Arg Ala Lys Ser Thr Leu Tyr Lys Tyr Val His Ser
35 40 45

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Val Ala Gly Ser Gln Glu Gly Cys Ser Ser Glu Val Ile Asn Phe Pro
1 5 10 15

His Ser His Lys Thr Arg Asp Tyr Val Ile Ile Lys Thr Lys Leu Ser
20 25 30

Ala

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Val Lys Glu Arg Ala Arg Asn His Arg Asn Gly Phe His Leu Ile Ser
1 5 10 15

Tyr Arg Trp Leu Cys Ser Gly Val Val
20 25

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Ile Tyr Glu Tyr Gly Gly Glu Lys Arg Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Leu Glu Gly His Thr
1 5

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Pro Asp Phe Thr Asp Pro Thr Arg Arg Ser Arg Gly Thr Lys Leu Leu
1 5 10 15

Lys Ser Cys Gln Arg Val Ala
20

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Cys Gly Ala Ser Asn Gly Asp
1 5

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Asn Ser Pro Thr Phe Ser Glu Val
1 5

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Ala Ser Gly Thr Glu Asp Ala Asn Glu Glu Glu Ile Pro Gln Leu Phe
1 5 10 15

Arg Leu Cys Arg Leu Gln Thr Val Gln Glu Gly Phe Cys His Ile Glu
20 25 30

Glu His Trp
35

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Ala Glu Arg Thr Leu
1 5

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

Ser Tyr Gln Asn Arg Trp Arg Val Asn Ser Ser Asn Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Arg Asp Thr His Gln Val Arg Cys Arg Lys Tyr His Asp Asp Gly Thr
1 5 10 15

Gly Phe Gly Ile Ser Gln
20

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Arg Arg Arg Lys Arg Asn His Trp Cys Leu Trp Thr Trp Trp Gly Trp
1 5 10 15

Glu Asp Asn Val Asn Ala Glu His
20

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Gln Arg Ala Asp His Lys Arg Thr Ser Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 55 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Cys Thr Asp Leu Gly Ser Asn Val Gln Arg Ile Arg Arg Val Tyr Asn
1 5 10 15

Ser Ala Ser Arg Trp Ser Thr Val Gly Phe Ile Leu Gly Arg Glu Gly
20 25 30

Asp Arg Arg Lys Gln Ser Phe Glu Asp Ile Gln Ser Phe Glu Thr Glu
35 40 45

Thr Phe Leu Val Val Ala Arg
50 55

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Cys Leu Gly Arg Asp Arg Leu Gly Glu Asn Trp Ser Ser Ser Thr
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Arg Asp Arg Arg Arg Val Asp Pro Cys
1 5

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Gln Gly Lys Gln Met Gln Gly Asp Val His Asp Thr Val Tyr Ser Ile
1 5 10 15

Met Gln Gln Tyr Gly Cys Gly Ile Gln Val Glu Ser Gly Val Ser Gly
20 25 30

Glu Glu Thr Arg Val Gly Ala Val Leu
35 40

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

Gly Met Glu Lys Arg Ser Phe Arg Val Ile Ile Asn Ser Pro Ala Arg
1 5 10 15

Gly Asp Tyr Ser Glu
20

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Met Trp Arg Ile Ala Thr Ser Val Asp His Phe Arg Arg Ser His Gly
1 5 10 15

Ser

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Ile Ser Ser Arg Asp Glu Gly Tyr Glu Leu Cys Ile Cys Pro Phe Glu
1 5 10 15

Ile Gln Leu Arg Gln Pro Arg Glu
20

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Ser Ala Ser Val Leu Phe Leu Val Leu Arg Phe Ile Pro Arg Arg Thr
1 5 10 15

Phe Tyr Arg Asp Arg Ala Ala Cys
20

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

Val Leu Gly Arg Arg Arg Val Ser His Gln Leu Pro Trp Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

His His Leu Gln Gly Ile Phe Ser His Trp Gly Ser Glu Ser Gly Met
1 5 10 15

Phe Val Gly Asn Arg Arg
20

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

Glu Asn Thr Gly Glu Asp Ala
1 5

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 43 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

Lys Thr His Met Pro Glu Thr Asp Asn Thr Asp Ala Pro Thr Glu Gly
1 5 10 15

Leu Phe Glu Glu Asp Ser Asn Arg Val Phe His Ala Tyr Ala Cys Ser
20 25 30

Gln Ser Leu Gly Leu Val Val His Lys Tyr His
35 40

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

Cys Gly Gln Lys Leu Cys Ile Val Asp Gly Ile
1 5 10

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Gly Ala Asp Pro Ser
1 5

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

Ser Arg Lys Leu Ala Thr Ser Val Gly Asp Leu Ile Val Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

Gln Asn Pro Asp Leu Ala
1 5

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

Asp Ser Val Val Tyr Gln Val Phe Gly Gly Val Val Ser Ser Val Tyr
1 5 10 15

Val Arg Asn Lys Asp Lys Cys Ile Ala Thr Gly Ala Trp Glu Ser
20 25 30

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

Lys Thr Glu Ala Ser Gly Pro Thr Lys Asn Ser Val Ser Ser Asp Asp
1 5 10 15

Pro Thr Arg Cys His Met Leu Ala Glu Gln Ala Arg Gly Ser Glu Leu
20 25 30

Val Leu Gln Leu Arg Arg Leu Gly Thr Ala Glu Leu Trp Arg Arg
35 40 45

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Ser Arg Arg Thr Arg Ile Arg
1 5

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Leu Gly Ile Leu Gly Lys Pro Asn His Thr Arg Tyr His Cys Ser Leu
1 5 10 15

Ile Gly Asp Pro Lys Asn Ser Leu Arg Val Arg Cys Phe Ala
20 25 30

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

Thr Tyr Thr Ala Ser Pro Arg
1 5

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

Thr Pro Leu Leu Gln Ser Pro Ile Thr His
1 5 10

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

Pro Trp Gln Glu Pro Glu Lys Thr
1 5

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

Leu Gly Val Pro Gly His Thr Arg Arg Phe
1 5 10

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 58 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

Leu Ala Ser Glu Ser Arg Gly Ser Asp Val Thr Gln Pro Ser Gln Leu
1 5 10 15

Asn Gln Ser Val Gly Lys Phe Cys Lys Pro Arg Leu Ser Ala Glu Tyr
20 25 30

Pro Leu His Lys His Phe Thr Leu Gln Gln Ala Glu Glu Cys Leu Met
35 40 45

Gly Ser Glu Thr Pro Lys Ala Arg Gly Asp
50 55

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

Thr Val Arg Leu Gln Arg Asp Arg Gly Ile Asp Lys Arg Thr Arg Glu
1 5 10 15

Ser Ile Arg Arg Arg Ser Asn Ile Val Pro Lys Pro Glu Asp Leu Glu
20 25 30

Asn

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

Gly Ser Ala Arg Thr Lys Gln His Pro Pro Ile Ser Ile Phe Ile Pro
1 5 10 15

Lys Ser

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

Asn Ile Ser His His Lys Leu Pro Gln Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

Glu Thr Ala Val Ser Gly Glu Glu Asp Pro Asp Glu Leu Ala Asn Ser
1 5 10 15

Leu Leu

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

Thr Ser His His
1

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

Glu Leu Arg Ala Leu Cys Thr Asn Met Ser Ile His Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

Gln Glu Ala Arg Lys Val Val Pro Val Lys Ser Ser Thr Phe His Ile
1 5 10 15

Ala Thr Lys Leu Glu Ile Met
20

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

Lys Pro Asn Tyr Pro Arg
1 5

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1491 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

ATCGATTGAT CTCTGGCTCA GTGCGAGTAG TCCATTTGAG AGCAGTCGTA GCCCCGCGTG 60

GCGCATCATG GAGCTATTTG GAATTTTCGC AGGGTTATCG ATTCGTAGTG GGAACCCATT 120

CATTGTTTGG AACCACCAAC GGACGACTTA ACAAGCTCCC CGAGGTGCAT GATGAAAATT 180

GCTCCAGTTG CCATAAATCA CAGCCCGCTC AGCAGGGAGG TCCCGTCACA CGCGGCACCC 240

ACTCAGGCAA AGCAAACCAA CCTTCAATCT GAAGCTGGCG ATTTAGATGC AAGAAAAAGT 300

AGCGCTTCAA GCCCGGAAAC CCGCGCATTA CTCGCTACTA AGACAGTACT CGGGAGACAC 360

AAGATAGAGG TTCCGGCCTT TGGAGGGTGG TTCAAAAAGA AATCATCTAA GCACGAGACG 420

GGCGGTTCAA GTGCCAACGC AGATAGTTCG AGCGTGGCTT CCGATTCCAC CGAAAAACCT 480

TTGTTCCGTC TCACGCACGT TCCTTACGTA TCCCAAGGTA ATGAGCGAAT GGGATGTTGG 540

TATGCCTGCG CAAGAATGGT TGGCCATTCT GTCGAAGCTG GGCCTCGCCT AGGGCTGCCG 600

GAGCTCTATG AGGGAAGGGA GGCGCCAGCT GGGCTACAAG ATTTTTCAGA TGTAGAAAGG 660

TTTATTCACA ATGAAGGATT AACTCGGGTA GACCTTCCAG ACAATGAGAG ATTTACACAC 720

GAAGAGTTGG GTGCACTGTT GTATAAGCAC GGGCCGATTA TATTTGGGTG GAAAACTCCG 780

AATGACAGCT GGCACATGTC GGTCCTCACT GGTGTCGATA AAGAGACGTC GTCCATTACT 840

TTTCACGATC CCCGACAGGG GCCGGACCTA GCAATGCCGC TCGATTACTT TAATCAGCGA 900

TTGGCATGGC AGGTTCCACA CGCAATGCTC TACCGCTAAG TAGCAGGGTA TCTTCACGTG 960

GCGGCATCAT GACAAGCCCA TGATGCCGCC AGCAGCTACC TGAATGCCGT CTGGCTTTTT 1020

GGTCCCTATT GTCGTATCCG GAAGATGACG TCAAAGAATC TCGGCAAGAG CTTTCTTGCT 1080

CGACTCCTCA GCTTCCGGAT CGATCAGGTC GCTTGCCAGA GCGCGCTTGT CCATGAGCAT 1140

CTGCCACAGC TGCTGGTCGA TGGTGTCCTC AGCTAAAGGG ATTTTGACGA CAACCATGCG 1200

CAACTGCCCG TTGCGATACG CTCGATCCTG AAGCCCCGGT GTCCATGGCA GCCCCAAGAA 1260

AAAGACATAG TTCGCCGCTG TGAGGTTGTA GCCTGTGCCG GCGGCCGACC TGGTCCCGAT 1320

AAACACCCTG CAGTCCGGAT CCTGCTGGAA AGCATCAATC GCCTTCTGCC GCTTCTTGGG 1380

CGAGTCACTG CCCACCAACG TCACGCACCC GACGCCAAGC TTGAGGCAGT GCTCCCGCAA 1440

CGTGGCCACG GATTCCTGAT ACTCGCAGAA GAGGATCACC TTGTCGTCGA C 1491

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 255 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

Met Lys Ile Ala Pro Val Ala Ile Asn His Ser Pro Leu Ser Arg Glu
1 5 10 15

Val Pro Ser His Ala Ala Pro Thr Gln Ala Lys Gln Thr Asn Leu Gln
20 25 30

Ser Glu Ala Gly Asp Leu Asp Ala Arg Lys Ser Ser Ala Ser Ser Pro
35 40 45

Glu Thr Arg Ala Leu Leu Ala Thr Lys Thr Val Leu Gly Arg His Lys
50 55 60

Ile Glu Val Pro Ala Phe Gly Gly Trp Phe Lys Lys Lys Ser Ser Lys
65 70 75 80

His Glu Thr Gly Gly Ser Ser Ala Asn Ala Asp Ser Ser Ser Val Ala
85 90 95

Ser Asp Ser Thr Glu Lys Pro Leu Phe Arg Leu Thr His Val Pro Tyr
100 105 110

Val Ser Gln Gly Asn Glu Arg Met Gly Cys Trp Tyr Ala Cys Ala Arg
115 120 125

Met Val Gly His Ser Val Glu Ala Gly Pro Arg Leu Gly Leu Pro Glu
130 135 140

Leu Tyr Glu Gly Arg Glu Ala Pro Ala Gly Leu Gln Asp Phe Ser Asp
145 150 155 160

Val Glu Arg Phe Ile His Asn Glu Gly Leu Thr Arg Val Asp Leu Pro
165 170 175

Asp Asn Glu Arg Phe Thr His Glu Glu Leu Gly Ala Leu Leu Tyr Lys

```
                180                 185                 190

His Gly Pro Ile Ile Phe Gly Trp Lys Thr Pro Asn Asp Ser Trp His
        195                 200                 205

Met Ser Val Leu Thr Gly Val Asp Lys Glu Thr Ser Ser Ile Thr Phe
    210                 215                 220

His Asp Pro Arg Gln Gly Pro Asp Leu Ala Met Pro Leu Asp Tyr Phe
225                 230                 235                 240

Asn Gln Arg Leu Ala Trp Gln Val Pro His Ala Met Leu Tyr Arg
                245                 250                 255
```

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1209 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

```
Met Asn Pro Ser Gly Ser Phe Pro Ser Val Glu Tyr Glu Val Phe Leu
1                   5                  10                  15

Ser Phe Arg Gly Pro Asp Thr Arg Glu Gln Phe Thr Asp Phe Leu Tyr
            20                  25                  30

Gln Ser Leu Arg Arg Tyr Lys Ile His Thr Phe Arg Asp Asp Asp Glu
        35                  40                  45

Leu Leu Lys Gly Lys Glu Ile Gly Pro Asn Leu Leu Arg Ala Ile Asp
    50                  55                  60

Gln Ser Lys Ile Tyr Val Pro Ile Ile Ser Ser Gly Tyr Ala Asp Ser
65                  70                  75                  80

Lys Trp Cys Leu Met Glu Leu Ala Glu Ile Val Arg Arg Gln Glu Glu
                85                  90                  95

Asp Pro Arg Arg Ile Ile Leu Pro Ile Phe Tyr Met Val Asp Pro Ser
            100                 105                 110

Asp Val Arg His Gln Thr Gly Cys Tyr Lys Lys Ala Phe Arg Lys His
        115                 120                 125

Ala Asn Lys Phe Asp Gly Gln Thr Ile Gln Asn Trp Lys Asp Ala Leu
    130                 135                 140

Lys Lys Val Gly Asp Leu Lys Gly Trp His Ile Gly Lys Asn Asp Lys
145                 150                 155                 160

Gln Gly Ala Ile Ala Asp Lys Val Ser Ala Asp Ile Trp Ser His Ile
                165                 170                 175
```

Ser Lys Glu Asn Leu Ile Leu Glu Thr Asp Glu Leu Val Gly Ile Asp
180 185 190

Asp His Ile Thr Ala Val Leu Glu Lys Leu Ser Leu Asp Ser Glu Asn
195 200 205

Val Thr Met Val Gly Leu Tyr Gly Met Gly Gly Ile Gly Lys Thr Thr
210 215 220

Thr Ala Lys Ala Val Tyr Asn Lys Ile Ser Ser Cys Phe Asp Cys Cys
225 230 235 240

Cys Phe Ile Asp Asn Ile Arg Glu Thr Gln Glu Lys Asp Gly Val Val
245 250 255

Val Leu Gln Lys Lys Leu Val Ser Glu Ile Leu Arg Ile Asp Ser Gly
260 265 270

Ser Val Gly Phe Asn Asn Asp Ser Gly Gly Arg Lys Thr Ile Lys Glu
275 280 285

Arg Val Ser Arg Phe Lys Ile Leu Val Val Leu Asp Asp Val Asp Glu
290 295 300

Lys Phe Lys Phe Glu Asp Met Leu Gly Ser Pro Lys Asp Phe Ile Ser
305 310 315 320

Gln Ser Arg Phe Ile Ile Thr Ser Arg Ser Met Arg Val Leu Gly Thr
325 330 335

Leu Asn Glu Asn Gln Cys Lys Leu Tyr Glu Val Gly Ser Met Ser Lys
340 345 350

Pro Arg Ser Leu Glu Leu Phe Ser Lys His Ala Phe Lys Lys Asn Thr
355 360 365

Pro Pro Ser Ser Tyr Tyr Glu Thr Leu Ala Asn Asp Val Val Asp Thr
370 375 380

Thr Ala Gly Leu Pro Leu Thr Leu Lys Val Ile Gly Ser Leu Leu Phe
385 390 395 400

Lys Gln Glu Ile Ala Val Trp Glu Asp Thr Leu Glu Gln Leu Arg Arg
405 410 415

Thr Leu Asn Leu Asp Glu Val Tyr Asp Arg Leu Lys Ile Ser Tyr Asp
420 425 430

Ala Leu Asn Pro Glu Ala Lys Glu Ile Phe Leu Asp Ile Ala Cys Phe
435 440 445

Phe Ile Gly Gln Asn Lys Glu Glu Pro Tyr Tyr Met Trp Thr Asp Cys
450 455 460

Asn Phe Tyr Pro Ala Ser Asn Ile Ile Phe Leu Ile Gln Arg Cys Met
465 470 475 480

Ile Gln Val Gly Asp Asp Asp Glu Phe Lys Met His Asp Gln Leu Arg
485 490 495

Asp Met Gly Arg Glu Ile Val Arg Arg Glu Asp Val Leu Pro Trp Lys
500 505 510

Ser Arg Ile Trp Ser Ala Glu Glu Gly Ile Asp Leu Leu Leu Asn Lys
515 520 525

Arg Lys Gly Ser Ser Lys Val Lys Ala Ile Ser Ile Pro Trp Gly Val
530 535 540

Lys Tyr Glu Phe Lys Ser Glu Cys Phe Leu Asn Leu Ser Glu Leu Arg
545 550 555 560

Tyr Leu His Ala Arg Glu Ala Met Leu Thr Gly Asp Phe Asn Asn Leu
565 570 575

Leu Pro Asn Leu Lys Trp Leu Glu Leu Pro Phe Tyr Lys His Gly Glu
580 585 590

Asp Asp Pro Pro Leu Thr Asn Tyr Thr Met Lys Asn Leu Ile Ile Val
595 600 605

Ile Leu Glu His Ser His Ile Thr Ala Asp Asp Trp Gly Gly Trp Arg
610 615 620

His Met Met Lys Met Ala Glu Arg Leu Lys Val Val Arg Leu Ala Ser
625 630 635 640

Asn Tyr Ser Leu Tyr Gly Arg Arg Val Arg Leu Ser Asp Cys Trp Arg
645 650 655

Phe Pro Lys Ser Ile Glu Val Leu Ser Met Thr Ala Ile Glu Met Asp
660 665 670

Glu Val Asp Ile Gly Glu Leu Lys Lys Leu Lys Thr Leu Val Leu Lys
675 680 685

Pro Cys Pro Ile Gln Lys Ile Ser Gly Gly Thr Phe Gly Met Leu Lys
690 695 700

Gly Leu Arg Glu Leu Cys Leu Glu Phe Asn Trp Gly Thr Asn Leu Arg
705 710 715 720

Glu Val Val Ala Asp Ile Gly Gln Leu Ser Ser Leu Lys Val Leu Lys
725 730 735

Thr Gly Ala Lys Glu Val Glu Ile Asn Glu Phe Pro Leu Gly Leu Lys
740 745 750

Thr Glu Leu Ser Thr Ser Ser Arg Ile Pro Asn Asn Leu Ser Gln Leu
755 760 765

Leu Asp Leu Glu Val Leu Lys Val Tyr Asp Cys Lys Asp Gly Phe Asp
770 775 780

Met Pro Pro Ala Ser Pro Ser Glu Asp Glu Ser Ser Val Trp Trp Lys
785 790 795 800

Val Ser Lys Leu Lys Ser Leu Gln Leu Glu Lys Thr Arg Ile Asn Val
805 810 815

Asn Val Val Asp Asp Ala Ser Ser Gly Gly His Leu Pro Arg Tyr Leu
820 825 830

Leu Pro Thr Ser Leu Thr Tyr Leu Lys Ile Tyr Gln Cys Thr Glu Pro
835 840 845

Thr Trp Leu Pro Gly Ile Glu Asn Leu Glu Asn Leu Thr Ser Leu Glu
850 855 860

Val Asn Asp Ile Phe Gln Thr Leu Gly Gly Asp Leu Asp Gly Leu Gln
865 870 875 880

Gly Leu Arg Ser Leu Glu Ile Leu Arg Ile Arg Lys Val Asn Gly Leu
885 890 895

Ala Arg Ile Lys Gly Leu Lys Asp Leu Leu Cys Ser Ser Thr Cys Lys
900 905 910

Leu Arg Lys Phe Tyr Ile Thr Glu Cys Pro Asp Leu Ile Glu Leu Leu
915 920 925

Pro Cys Glu Leu Gly Val Gln Thr Val Val Val Pro Ser Met Ala Glu
930 935 940

Leu Thr Ile Arg Asp Cys Pro Arg Leu Glu Val Gly Pro Met Ile Arg
945 950 955 960

Ser Leu Pro Lys Phe Pro Met Leu Lys Lys Leu Asp Leu Ala Val Ala
965 970 975

Asn Ile Thr Lys Glu Glu Asp Leu Asp Ala Ile Gly Ser Leu Glu Glu
980 985 990

Leu Val Ser Leu Glu Leu Glu Leu Asp Asp Thr Ser Ser Gly Ile Glu
995 1000 1005

Arg Ile Val Ser Ser Ser Lys Leu Gln Lys Leu Thr Thr Leu Val Val
1010 1015 1020

Lys Val Pro Ser Leu Arg Glu Ile Glu Gly Leu Glu Glu Leu Lys Ser
1025 1030 1035 1040

Leu Gln Asp Leu Tyr Leu Glu Gly Cys Thr Ser Leu Gly Arg Leu Pro
1045 1050 1055

Leu Glu Lys Leu Lys Glu Leu Asp Ile Gly Gly Cys Pro Asp Leu Thr
1060 1065 1070

Glu Leu Val Gln Thr Val Val Ala Val Pro Ser Leu Arg Gly Leu Thr
1075 1080 1085

Ile Arg Asp Cys Pro Arg Leu Glu Val Gly Pro Met Ile Gln Ser Leu
1090 1095 1100

Pro Lys Phe Pro Met Leu Asn Glu Leu Thr Leu Ser Met Val Asn Ile
1105 1110 1115 1120

Thr Lys Glu Asp Glu Leu Glu Val Leu Gly Ser Leu Glu Glu Leu Asp
1125 1130 1135

Ser Leu Glu Leu Thr Leu Asp Asp Thr Cys Ser Ser Ile Glu Arg Ile
1140 1145 1150

Ser Phe Leu Ser Lys Leu Gln Lys Leu Thr Thr Leu Ile Val Glu Val
1155 1160 1165

Pro Ser Leu Arg Glu Ile Glu Gly Leu Ala Glu Leu Lys Ser Leu Arg
1170 1175 1180

Ile Leu Tyr Leu Glu Gly Cys Thr Ser Leu Glu Arg Leu Trp Pro Asp
1185 1190 1195 1200

Gln Gln Gln Leu Gly Ser Leu Lys Asn
1205

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1143 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

Met Ala Ser Ser Ser Ser Ser Ser Arg Trp Ser Tyr Asp Val Phe Leu
1 5 10 15

Ser Phe Arg Gly Glu Asp Thr Arg Lys Thr Phe Thr Ser His Leu Tyr
20 25 30

Glu Val Leu Asn Asp Lys Gly Ile Lys Thr Phe Gln Asp Asp Lys Arg
35 40 45

Leu Glu Tyr Gly Ala Thr Ile Pro Gly Glu Leu Cys Lys Ala Ile Glu
50 55 60

Glu Ser Gln Phe Ala Ile Val Val Phe Ser Glu Asn Tyr Ala Thr Ser
65 70 75 80

Arg Trp Cys Leu Asn Glu Leu Val Lys Ile Met Glu Cys Lys Thr Arg
85 90 95

Phe Lys Gln Thr Val Ile Pro Ile Phe Tyr Asp Val Asp Pro Ser His
100 105 110

Val Arg Asn Gln Lys Glu Ser Phe Ala Lys Ala Phe Glu Glu His Glu
115 120 125

Thr Lys Tyr Lys Asp Asp Val Glu Gly Ile Gln Arg Trp Arg Ile Ala
130 135 140

Leu Asn Glu Ala Ala Asn Leu Lys Gly Ser Cys Asp Asn Arg Asp Lys
145 150 155 160

Thr Asp Ala Asp Cys Ile Arg Gln Ile Val Asp Gln Ile Ser Ser Lys
165 170 175

Leu Cys Lys Ile Ser Leu Ser Tyr Leu Gln Asn Ile Val Gly Ile Asp
180 185 190

Thr His Leu Glu Lys Ile Glu Ser Leu Leu Glu Ile Gly Ile Asn Gly
195 200 205

Val Arg Ile Met Gly Ile Trp Gly Met Gly Gly Val Gly Lys Thr Thr
210 215 220

Ile Ala Arg Ala Ile Phe Asp Thr Leu Leu Gly Arg Met Asp Ser Ser

225 230 235 240

Tyr Gln Phe Asp Gly Ala Cys Phe Leu Lys Asp Ile Lys Glu Asn Lys
245 250 255

Arg Gly Met His Ser Leu Gln Asn Ala Leu Leu Ser Glu Leu Leu Arg
260 265 270

Glu Lys Ala Asn Tyr Asn Asn Glu Glu Asp Gly Lys His Gln Met Ala
275 280 285

Ser Arg Leu Arg Ser Lys Lys Val Leu Ile Val Leu Asp Asp Ile Asp
290 295 300

Asn Lys Asp His Tyr Leu Glu Tyr Leu Ala Gly Asp Leu Asp Trp Phe
305 310 315 320

Gly Asn Gly Ser Arg Ile Ile Ile Thr Thr Arg Asp Lys His Leu Ile
325 330 335

Glu Lys Asn Asp Ile Ile Tyr Glu Val Thr Ala Leu Pro Asp His Glu
340 345 350

Ser Ile Gln Leu Phe Lys Gln His Ala Phe Gly Lys Glu Val Pro Asn
355 360 365

Glu Asn Phe Glu Lys Leu Ser Leu Glu Val Val Asn Tyr Ala Lys Gly
370 375 380

Leu Pro Leu Ala Leu Lys Val Trp Gly Ser Leu Leu His Asn Leu Arg
385 390 395 400

Leu Thr Glu Trp Lys Ser Ala Ile Glu His Met Lys Asn Asn Ser Tyr
405 410 415

Ser Gly Ile Ile Asp Lys Leu Lys Ile Ser Tyr Asp Gly Leu Glu Pro
420 425 430

Lys Gln Gln Glu Met Phe Leu Asp Ile Ala Cys Phe Leu Arg Gly Glu
435 440 445

Glu Lys Asp Tyr Ile Leu Gln Ile Leu Glu Ser Cys His Ile Gly Ala
450 455 460

Glu Tyr Gly Leu Arg Ile Leu Ile Asp Lys Ser Leu Val Phe Ile Ser
465 470 475 480

Glu Tyr Asn Gln Val Gln Met His Asp Leu Ile Gln Asp Met Gly Lys
485 490 495

Tyr Ile Val Asn Phe Gln Lys Asp Pro Gly Glu Arg Ser Arg Leu Trp
500 505 510

Leu Ala Lys Glu Val Glu Glu Val Met Ser Asn Asn Thr Gly Thr Met
515 520 525

Ala Met Glu Ala Ile Trp Val Ser Ser Tyr Ser Ser Thr Leu Arg Phe
530 535 540

Ser Asn Gln Ala Val Lys Asn Met Lys Arg Leu Arg Val Phe Asn Met
545 550 555 560

Gly Arg Ser Ser Thr His Tyr Ala Ile Asp Tyr Leu Pro Asn Asn Leu

565 570 575

Arg Cys Phe Val Cys Thr Asn Tyr Pro Trp Glu Ser Phe Pro Ser Thr
580 585 590

Phe Glu Leu Lys Met Leu Val His Leu Gln Leu Arg His Asn Ser Leu
595 600 605

Arg His Leu Trp Thr Glu Thr Lys His Leu Pro Ser Leu Arg Arg Ile
610 615 620

Asp Leu Ser Trp Ser Lys Arg Leu Thr Arg Thr Pro Asp Phe Thr Gly
625 630 635 640

Met Pro Asn Leu Glu Tyr Val Asn Leu Tyr Gln Cys Ser Asn Leu Glu
645 650 655

Glu Val His His Ser Leu Gly Cys Cys Ser Lys Val Ile Gly Leu Tyr
660 665 670

Leu Asn Asp Cys Lys Ser Leu Lys Arg Phe Pro Cys Val Asn Val Glu
675 680 685

Ser Leu Glu Tyr Leu Gly Leu Arg Ser Cys Asp Ser Leu Glu Lys Leu
690 695 700

Pro Glu Ile Tyr Gly Arg Met Lys Pro Glu Ile Gln Ile His Met Gln
705 710 715 720

Gly Ser Gly Ile Arg Glu Leu Pro Ser Ser Ile Phe Gln Tyr Lys Thr
725 730 735

His Val Thr Lys Leu Leu Leu Trp Asn Met Lys Asn Leu Val Ala Leu
740 745 750

Pro Ser Ser Ile Cys Arg Leu Lys Ser Leu Val Ser Leu Ser Val Ser
755 760 765

Gly Cys Ser Lys Leu Glu Ser Leu Pro Glu Glu Ile Gly Asp Leu Asp
770 775 780

Asn Leu Arg Val Phe Asp Ala Ser Asp Thr Leu Ile Leu Arg Pro Pro
785 790 795 800

Ser Ser Ile Ile Arg Leu Asn Lys Leu Ile Ile Leu Met Phe Arg Gly
805 810 815

Phe Lys Asp Gly Val His Phe Glu Phe Pro Pro Val Ala Glu Gly Leu
820 825 830

His Ser Leu Glu Tyr Leu Asn Leu Ser Tyr Cys Asn Leu Ile Asp Gly
835 840 845

Gly Leu Pro Glu Glu Ile Gly Ser Leu Ser Ser Leu Lys Lys Leu Asp
850 855 860

Leu Ser Arg Asn Asn Phe Glu His Leu Pro Ser Ser Ile Ala Gln Leu
865 870 875 880

Gly Ala Leu Gln Ser Leu Asp Leu Lys Asp Cys Gln Arg Leu Thr Gln
885 890 895

Leu Pro Glu Leu Pro Pro Glu Leu Asn Glu Leu His Val Asp Cys His

900 905 910

Met Ala Leu Lys Phe Ile His Tyr Leu Val Thr Lys Arg Lys Lys Leu
915 920 925

His Arg Val Lys Leu Asp Asp Ala His Asn Asp Thr Met Tyr Asn Leu
930 935 940

Phe Ala Tyr Thr Met Phe Gln Asn Ile Ser Ser Met Arg His Asp Ile
945 950 955 960

Ser Ala Ser Asp Ser Leu Ser Leu Thr Val Phe Thr Gly Gln Pro Tyr
965 970 975

Pro Glu Lys Ile Pro Ser Trp Phe His His Gln Gly Trp Asp Ser Ser
980 985 990

Val Ser Val Asn Leu Pro Glu Asn Trp Tyr Ile Pro Asp Lys Phe Leu
995 1000 1005

Gly Phe Ala Val Cys Tyr Ser Arg Ser Leu Ile Asp Thr Thr Ala His
1010 1015 1020

Leu Ile Pro Val Cys Asp Asp Lys Met Ser Arg Met Thr Gln Lys Leu
1025 1030 1035 1040

Ala Leu Ser Glu Cys Asp Thr Glu Ser Ser Asn Tyr Ser Glu Trp Asp
1045 1050 1055

Ile His Phe Phe Phe Val Pro Phe Ala Gly Leu Trp Asp Thr Ser Lys
1060 1065 1070

Ala Asn Gly Lys Thr Pro Asn Asp Tyr Gly Ile Ile Arg Leu Ser Phe
1075 1080 1085

Ser Gly Glu Glu Lys Met Tyr Gly Arg Leu Arg Leu Tyr Lys Glu Gly
1090 1095 1100

Pro Glu Val Asn Ala Leu Leu Gln Met Arg Glu Asn Ser Asn Glu Pro
1105 1110 1115 1120

Thr Glu His Ser Thr Gly Ile Arg Arg Thr Gln Tyr Asn Asn Arg Thr
1125 1130 1135

Ser Phe Tyr Glu Leu Ile Asn
1140

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 429 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

Leu Arg Ser Lys Leu Asp Leu Ile Ile Asp Leu Lys His Gln Ile Glu
1 5 10 15

Ser Val Lys Glu Gly Leu Leu Cys Leu Arg Ser Phe Ile Asp His Phe
20 25 30

Ser Glu Ser Tyr Val Glu His Asp Glu Ala Cys Gly Leu Ile Ala Arg
35 40 45

Val Ser Val Met Ala Tyr Lys Ala Glu Tyr Val Ile Asp Ser Cys Leu
50 55 60

Ala Tyr Ser His Pro Leu Trp Tyr Lys Val Leu Trp Ile Ser Glu Val
65 70 75 80

Leu Glu Asn Ile Lys Leu Val Asn Lys Val Val Gly Glu Thr Cys Glu
85 90 95

Arg Arg Asn Thr Glu Val Thr Val His Glu Val Ala Lys Thr Thr Thr
100 105 110

Asn Val Ala Pro Ser Phe Ser Ala Tyr Thr Gln Arg Ala Asn Glu Glu
115 120 125

Met Glu Gly Phe Gln Asp Thr Ile Asp Glu Leu Lys Asp Lys Leu Leu
130 135 140

Gly Gly Ser Pro Glu Leu Asp Val Ile Ser Ile Val Gly Met Pro Gly
145 150 155 160

Leu Gly Lys Thr Thr Leu Ala Lys Lys Ile Tyr Asn Asp Pro Glu Val
165 170 175

Thr Ser Arg Phe Asp Val His Ala Gln Cys Val Val Thr Gln Leu Tyr
180 185 190

Ser Trp Arg Glu Leu Leu Leu Thr Ile Leu Asn Asp Val Leu Glu Pro
195 200 205

Ser Asp Arg Asn Glu Lys Glu Asp Gly Glu Ile Ala Asp Glu Leu Arg
210 215 220

Arg Phe Leu Leu Thr Lys Arg Phe Leu Ile Leu Ile Asp Asp Val Trp
225 230 235 240

Asp Tyr Lys Val Trp Asp Asn Leu Cys Met Cys Phe Ser Asp Val Ser
245 250 255

Asn Arg Ser Arg Ile Ile Leu Thr Thr Arg Leu Asn Asp Val Ala Glu
260 265 270

Tyr Val Lys Cys Glu Ser Asp Pro His His Leu Arg Leu Phe Arg Asp
275 280 285

Asp Glu Ser Trp Thr Leu Leu Gln Lys Glu Val Phe Gln Gly Glu Ser
290 295 300

Cys Pro Pro Glu Leu Glu Asp Val Gly Phe Glu Ile Ser Lys Ser Cys
305 310 315 320

Arg Gly Leu Pro Leu Ser Val Val Leu Val Ala Gly Val Leu Lys Gln
325 330 335

Lys Lys Lys Thr Leu Asp Ser Trp Lys Val Val Glu Gln Ser Leu Ser
340 345 350

Ser Gln Arg Ile Gly Ser Leu Glu Glu Ser Ile Ser Ile Ile Gly Phe
355 360 365

Ser Tyr Lys Asn Leu Pro His Tyr Leu Lys Pro Cys Phe Leu Tyr Phe
370 375 380

Gly Gly Phe Leu Gln Gly Lys Asp Ile His Asp Ser Lys Met Thr Lys
385 390 395 400

Leu Trp Val Ala Glu Glu Phe Val Gln Ala Asn Asn Glu Lys Gly Gln
405 410 415

Glu Asp Thr Arg Thr Arg Phe Leu Gly Arg Ser Tyr Trp
420 425

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

Gly Met Gly Gly Ile Gly Lys Thr Thr Thr Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

Gly Met Gly Gly Val Gly Lys Thr Thr Ile Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

Gly Met Pro Gly Leu Gly Lys Thr Thr Leu Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

Gly Pro Gly Gly Val Gly Lys Thr Thr Leu Met
1 5 10

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

Phe Lys Ile Leu Val Val Leu Asp Asp Val Asp
1 5 10

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

Lys Lys Val Leu Ile Val Leu Asp Asp Ile Asp
1 5 10

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

Lys Arg Phe Leu Ile Leu Ile Asp Asp Val Trp
1 5 10

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

Lys Arg Phe Leu Leu Leu Leu Asp Asp Val Trp
1 5 10

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

Ser Arg Phe Ile Ile Thr Ser Arg
1 5

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

Ser Arg Ile Ile Ile Thr Thr Arg
1 5

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

Ser Arg Ile Ile Leu Thr Thr Arg
1 5

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

Thr Thr Arg
1

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

Gly Leu Pro Leu Thr Leu Lys Val
1 5

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

Gly Leu Pro Leu Ala Leu Lys Val
1 5

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

Gly Leu Pro Leu Ser Val Val Leu
1 5

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Gly Leu Pro Leu Ala Leu Ile Thr
1 5

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

Lys Ile Ser Tyr Asp Ala Leu
1 5

(2) INFORMATION FOR SEQ ID NO:127:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

Lys Ile Ser Tyr Asp Gly Leu
1 5

(2) INFORMATION FOR SEQ ID NO:128:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

Gly Phe Ser Tyr Lys Asn Leu
1 5

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

Val Phe Leu Ser Phe Arg Gly
1 5

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

Pro Ile Phe Tyr Met Val Asp Pro
1 5

(2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

Pro Ile Phe Tyr Asp Val Asp Pro
1 5

(2) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

Val Gly Ile Asp Asp His
1 5

(2) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

Val Gly Ile Asp Thr His
1 5

(2) INFORMATION FOR SEQ ID NO:134:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

Phe Leu Asp Ile Ala Cys Phe
1 5

(2) INFORMATION FOR SEQ ID NO:135:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

Met His Asp Gln Leu Arg Asp Met Gly
1 5

(2) INFORMATION FOR SEQ ID NO:136:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

Met His Asp Leu Ile Gln Asp Met Gly
1 5

(2) INFORMATION FOR SEQ ID NO:137:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

Met His Asp Leu Ile Gln Asp Met Gly
1 5

(2) INFORMATION FOR SEQ ID NO:138:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:

Ser Lys Leu Glu Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:139:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

Gly Leu His Ser Leu Glu Tyr Leu
1 5

(2) INFORMATION FOR SEQ ID NO:140:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 base pairs
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

Gly Leu Arg Ser Leu Glu Ile Leu
1 5

(2) INFORMATION FOR SEQ ID NO:141:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3432 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:

ACAAGTAAAA GAAAGAGCGA GAAATCATCG AAATGGATTT CATCTCATCT CTTATCGTTG 60

GCTGTGCTCA GGTGTTGTGT GAATCTATGA ATATGGCGGA GAGAAGAGGA CATAAGACTG 120

ATCTTAGACA AGCCATCACT GATCTTGAAA CAGCCATCGG TGACTTGAAG GCCATACGTG 180

ATGACCTGAC TTTACGGATC CAACAAGACG GTCTAGAGGG ACGAAGCTGC TCAAATCGTG 240

CCAGAGAGTG GCTTAGTGCG GTGCAAGTAA CGGAGACTAA AACAGCCCTA CTTTTAGTGA 300

GGTTTAGGCG TCGGGAACAG AGGACGCGAA TGAGGAGGAG ATACCTCAGT TGTTTCGGTT 360

GTGCCGACTA CAAACTGTGC AAGAAGGTTT CTGCCATATT GAAGAGCATT GGTGAGCTGA 420

GAGAACGCTC TGAAGCTATC AAAACAGATG GCGGGTCAAT TCAAGTAACT TGTAGAGAGA 480

TACCCATCAA GTCCGTTGTC GGAAATACCA CGATGATGGA ACAGGTTTTG GAATTTCTCA 540

GTGAAGAAGA AGAAAGAGGA ATCATTGGTG TTTATGGACC TGGTGGGGTT GGGAAGACAA 600

CGTTAATGCA GAGCATTAAC AACGAGCTGA TCACAAAAGG ACATCAGTAT GATGTACTGA 660

TTTGGGTTCA AATGTCCAGA GAATTCGGCG AGTGTACAAT TCAGCAAGCC GTTGGAGCAC 720

GGTTGGGTTT ATCTTGGGAC GAGAAGGAGA CCGGCGAAAA CAGAGCTTTG AAGATATACA 780

GAGCTTTGAG ACAGAAACGT TTCTTGTTGT TGCTAGATGA GTCTGGGAAG AGATAGACTT 840

GGAGAAAACT GGAGTTCCTC GACCTTGACA GGGAAAACAA ATGCAAGGTG ATGTTCACGA 900

CACGGTCTAT AGCATTATGC AACAATATGG GTGCGGAATA CAAGTTGAGA GTGGAGTTTC 960

TGGAGAAGAA ACACGCGTGG GAGCTGTTCT GTAGTAAGGT ATGGAGAAAA GATCTTTTAG 1020

AGTCATCATC AATTCGCCGG CTCGCGGAGA TTATAGTGAG TAAATGTGGA GGATTGCCAC 1080

TAGCGTTGAT CACTTTAGGA GGAGCCATGG CTCATAGAGA GACAGAAGAA GAGTGGATCC 1140

ATGCTAGTGA AGTTCTGACT AGATTTCCAG CAGAGATGAA GGGTATGAAC TATGTATTTG 1200

CCCTTTTGAA ATTCAGCTAC GACAACCTCG AGAGTGATCT GCTTCGGTCT TGTTTCTTGT 1260

ACTGCGCTTT ATTCCCAGAA GAACATTGTA TAGAGATCGA GCAGCTTGTT CAGTACTGGG 1320

TCGGCGAAGG GTTTCTCACC AGCTCCCATG GCGTTAACAC CATTTACAAG GGATATTTTC 1380

TCATTGGGGA TCTGAAAGCG GCATGTTTGT TGGAAACCGG AGATGAGAAA ACACAGGTGA 1440

AGATGCATAA TGTGGTCAGA AGCTTTGCAT TGTGGATGGC ATCTGAACAG GGGACTTATA 1500

AGGAGCTGAT CCTAGTTGAG CCTAGCATGG GACATACTGA AGCTCCTAAA GCAGAAAACT 1560

GGCGACAAGC TTGGTGATCT CATTGTTAGA TAACAGAATC CAGACCTTGC CTGAAAAACT 1620

CATATGCCCG AAACTGACAA CACTGATGCT CCAACAGAAC AGCTCTTTGA AGAAGATTCC 1680

AACAGGGTTT TTCATGCATA TGCCTGTTCT CAGAGTCTTG GACTTGTCGT TCACAAGTAT 1740

CACTGAGATT CCGTTGTCTA TCAAGTATTT GGTGGAGTTG TATCATCTGT CTATGTCAGG 1800

AACAAAGATA AGTGTATTGC CACAGGAGCT TGGGAATCTT AGAAAACTGA AGCATCTGGA 1860

CCTACAAAGA ACTCAGTTTC TTCAGACGAT CCCACGAGAT GCCATATGTT GGCTGAGCAA 1920

GCTCGAGGTT CTGAACTTGT ACTACAGTTA CGCCGGTTGG GAACTGCAGA GCTTTGGAGA 1980

AGATGAAGCA GAAGAACTCG GATTCGCTGA CTTGGAATAC TTGGAAAACC TAACCACACT 2040

CGGTATCACT GTTCTCTCAT TGGAGACCCT AAAAACTCTC TTCGAGTTCG GTGCTTTGCA 2100

TAAACATATA CAGCATCTCC ACGTTGAAGA GTGCAATGAA CTCCTCTACT TCAATCTCCC 2160

ATCACTCACT AACCATGGCA GGAACCTGAG AAGACTTAGC ATTAAAAGTT GCCATGACTT 2220

GGAGTACCTG GTCACACCCG CAGATTTTGA AAATGATTGG CTTCCGAGTC TAGAGGTTCT 2280

GACGTTACAC AGCCTTCACA ACTTAACCAG AGTGTGGGGA AATTCTGTAA GCCAAGATTG 2340

TCTGCGGAAT ATCCGTTGCA TAAACATTTC ACACTGCAAC AAGCTGAAGA ATGTCTCATG 2400

GGTTCAGAAA CTCCCAAAGC TAGAGGTGAT TGAACTGTTC GACTGCAGAG AGATAGAGGA 2460

ATTGATAAGC GAACACGAGA GTCCATCCGT CGAAGATCCA ACATTGTTCC CAAGCCTGAA 2520

GACCTTGAGA ACTAGGGATC TGCCAGAACT AAACAGCATC CTCCCATCTC GATTTTCATT 2580

CCAAAAAGTT GAAACATTAG TCATCACAAA TTGCCCCAGA GTTAAGAAAC TGCCGTTTCA 2640

GGAGAGGAGG ACCCAGATGA ACTTGCCAAC AGTTTATTGT GAGGAGAAAT GGTGGAAAGC 2700

ACTGGAAAAA GTTGAAACAT TAGTCATCAC AAATTGCCCC AGAGTTAAGA AACTGCCGTT 2760

TCAGGAGAGG AGGACCCAGA TGAACTTGCC AACAGTTTAT TGTGAGGAGA AATGGTGGAA 2820

AGCACTGGAA AAAGATCAAC CAAACGAAGA GCTTTGTTAT TTACCGCGCT TTGTTCCAAA 2880

TTGATATAAG AGCTAAGAGC ACTCTGTACA AATATGTCCA TTCATAAGTA GCAGGAAGCC 2940

AGGAAGGTTG TTCCAGTGAA GTCATCAACT TTCCACTAGA CCACAAAACT AGAGATTATG 3000

TAATCATAAA AACCAAACTA TCCGCGATCA AATAGATCTC ACGACTATGA GGACGAAGAC 3060

TCACCGAGTA TCGTCGATAT AGAAACTCCA AGCTCCAGTT CCGATCAGTG AAGACGAACA 3120

AGTTTATCAG ATCTCTGCAA CAATTCTGGG AATCGTCACC TCAGATTAGA CCTCCAGTAA 3180

GAAGTGAGAA AGCATGGACG ACGACTGTGA AGAATTGAGC TAATGAGCTG AACCGGATCC 3240

GGTGAAATTG CAGAACCGGA TCGGAGAAGA AGAATTTTGC ATTTGTGCAT CTTTATTTTT 3300

AATTGTTACG TTTGAGCCCC AATAATCATA GATATTGTAG TGAAGACCAA ATTTCATGGT 3360

GGATCAATCA AATTGTATTT TCAAATTTTC GTAGTGTAAT AACGGAAAAA GGAATAAAAA 3420

GGTCACTGAG TA 3432

(2) INFORMATION FOR SEQ ID NO:142:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 909 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:

Met Asp Phe Ile Ser Ser Leu Ile Val Gly Cys Ala Gln Val Leu Cys
1 5 10 15

Glu Ser Met Asn Met Ala Glu Arg Arg Gly His Lys Thr Asp Leu Arg
20 25 30

Gln Ala Ile Thr Asp Leu Glu Thr Ala Ile Gly Asp Leu Lys Ala Ile
35 40 45

Arg Asp Asp Leu Thr Leu Arg Ile Gln Gln Asp Gly Leu Glu Gly Arg
50 55 60

Ser Cys Ser Asn Arg Ala Arg Glu Trp Leu Ser Ala Val Gln Val Thr
65 70 75 80

Glu Thr Lys Thr Ala Leu Leu Leu Val Arg Phe Arg Arg Arg Glu Gln

85 90 95

Arg Thr Arg Met Arg Arg Arg Tyr Leu Ser Cys Phe Gly Cys Ala Asp
100 105 110

Tyr Lys Leu Cys Lys Lys Val Ser Ala Ile Leu Lys Ser Ile Gly Glu
115 120 125

Leu Arg Glu Arg Ser Glu Ala Ile Lys Thr Asp Gly Gly Ser Ile Gln
130 135 140

Val Thr Cys Arg Glu Ile Pro Ile Lys Ser Val Val Gly Asn Thr Thr
145 150 155 160

Met Met Glu Gln Val Leu Glu Phe Leu Ser Glu Glu Glu Glu Arg Gly
165 170 175

Ile Ile Gly Val Tyr Gly Pro Gly Gly Val Gly Lys Thr Thr Leu Met
180 185 190

Gln Ser Ile Asn Asn Glu Leu Ile Thr Lys Gly His Gln Tyr Asp Val
195 200 205

Leu Ile Trp Val Gln Met Ser Arg Glu Phe Gly Glu Cys Thr Ile Gln
210 215 220

Gln Ala Val Gly Ala Arg Leu Gly Leu Ser Trp Asp Glu Lys Glu Thr
225 230 235 240

Gly Glu Asn Arg Ala Leu Lys Ile Tyr Arg Ala Leu Arg Gln Lys Arg
245 250 255

Phe Leu Leu Leu Leu Asp Asp Val Trp Glu Glu Ile Asp Leu Glu Lys
260 265 270

Thr Gly Val Pro Arg Pro Asp Arg Glu Asn Lys Cys Lys Val Met Phe
275 280 285

Thr Thr Arg Ser Ile Ala Leu Cys Asn Asn Met Gly Ala Glu Tyr Lys
290 295 300

Leu Arg Val Glu Phe Leu Glu Lys Lys His Ala Trp Glu Leu Phe Cys
305 310 315 320

Ser Lys Val Trp Arg Lys Asp Leu Leu Glu Ser Ser Ser Ile Arg Arg
325 330 335

Leu Ala Glu Ile Ile Val Ser Lys Cys Gly Gly Leu Pro Leu Ala Leu
340 345 350

Ile Thr Leu Gly Gly Ala Met Ala His Arg Glu Thr Glu Glu Glu Trp
355 360 365

Ile His Ala Ser Glu Val Leu Thr Arg Phe Pro Ala Glu Met Lys Gly
370 375 380

Met Asn Tyr Val Phe Ala Leu Leu Lys Phe Ser Tyr Asp Asn Leu Glu
385 390 395 400

Ser Asp Leu Leu Arg Ser Cys Phe Leu Tyr Cys Ala Leu Phe Pro Glu
405 410 415

Glu His Ser Ile Glu Ile Glu Gln Leu Val Glu Tyr Trp Val Gly Glu

420 425 430

Gly Phe Leu Thr Ser Ser His Gly Val Asn Thr Ile Tyr Lys Gly Tyr
435 440 445

Phe Leu Ile Gly Asp Leu Lys Ala Ala Cys Leu Leu Glu Thr Gly Asp
450 455 460

Glu Lys Thr Gln Val Lys Met His Asn Val Val Arg Ser Phe Ala Leu
465 470 475 480

Trp Met Ala Ser Glu Gln Gly Thr Tyr Lys Glu Leu Ile Leu Val Glu
485 490 495

Pro Ser Met Gly His Thr Glu Ala Pro Lys Ala Glu Asn Trp Arg Gln
500 505 510

Ala Leu Val Ile Ser Leu Leu Asp Asn Arg Ile Gln Thr Leu Pro Glu
515 520 525

Lys Leu Ile Cys Pro Lys Leu Thr Thr Leu Met Leu Gln Gln Asn Ser
530 535 540

Ser Leu Lys Lys Ile Pro Thr Gly Phe Phe Met His Met Pro Val Leu
545 550 555 560

Arg Val Leu Asp Leu Ser Phe Thr Ser Ile Thr Glu Ile Pro Leu Ser
565 570 575

Ile Lys Tyr Leu Val Glu Leu Tyr His Leu Ser Met Ser Gly Thr Lys
580 585 590

Ile Ser Val Leu Pro Gln Glu Leu Gly Asn Leu Arg Lys Leu Lys His
595 600 605

Leu Asp Leu Gln Arg Thr Gln Phe Leu Gln Thr Ile Pro Arg Asp Ala
610 615 620

Ile Cys Trp Leu Ser Lys Leu Glu Val Leu Asn Leu Tyr Tyr Ser Tyr
625 630 635 640

Ala Gly Trp Glu Leu Gln Ser Phe Gly Glu Asp Glu Ala Glu Glu Leu
645 650 655

Gly Phe Ala Asp Leu Glu Tyr Leu Glu Asn Leu Thr Thr Leu Gly Ile
660 665 670

Thr Val Leu Ser Leu Glu Thr Leu Lys Thr Leu Phe Glu Phe Gly Ala
675 680 685

Leu His Lys His Ile Gln His Leu His Val Glu Glu Cys Asn Glu Leu
690 695 700

Leu Tyr Phe Asn Leu Pro Ser Leu Thr Asn His Gly Arg Asn Leu Arg
705 710 715 720

Arg Leu Ser Ile Lys Ser Cys His Asp Leu Glu Tyr Leu Val Thr Pro
725 730 735

Ala Asp Phe Glu Asn Asp Trp Leu Pro Ser Leu Glu Val Leu Thr Leu
740 745 750

His Ser Leu His Asn Leu Thr Arg Val Trp Gly Asn Ser Val Ser Gln

```
          755                 760                 765

Asp Cys Leu Arg Asn Ile Arg Cys Ile Asn Ile Ser His Cys Asn Lys
     770                 775                 780

Leu Lys Asn Val Ser Trp Val Gln Lys Leu Pro Lys Leu Glu Val Ile
785                 790                 795                 800

Glu Leu Phe Asp Cys Arg Glu Ile Glu Glu Leu Ile Ser Glu His Glu
                805                 810                 815

Ser Pro Ser Val Glu Asp Pro Thr Leu Phe Pro Ser Leu Lys Thr Leu
          820                 825                 830

Arg Thr Arg Asp Leu Pro Glu Leu Asn Ser Ile Leu Pro Ser Arg Phe
          835                 840                 845

Ser Phe Gln Lys Val Glu Thr Leu Val Ile Thr Asn Cys Pro Arg Val
     850                 855                 860

Lys Lys Leu Pro Phe Gln Glu Arg Arg Thr Gln Met Asn Leu Pro Thr
865                 870                 875                 880

Val Tyr Cys Glu Glu Lys Trp Trp Lys Ala Leu Glu Lys Asp Gln Pro
                885                 890                 895

Asn Glu Glu Leu Cys Tyr Leu Pro Arg Phe Val Pro Asn
          900                 905
```

(2) INFORMATION FOR SEQ ID NO:143:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

```
Pro Lys Ala Glu Asn Trp Arg Gln Ala Leu Val Ile Ser Leu Leu Asp
1               5                  10                  15

Asn Arg Ile Gln Thr Leu
            20
```

(2) INFORMATION FOR SEQ ID NO:144:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:

Pro Glu Lys Leu Ile Cys Pro Lys Leu Thr Thr Leu Met Leu Gln Gln
1 5 10 15

Asn Ser Ser Leu Lys Lys Ile
20

(2) INFORMATION FOR SEQ ID NO:145:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:

Pro Thr Gly Phe Phe Met His Met Pro Val Leu Arg Val Leu Asp Leu
1 5 10 15

Ser Phe Thr Ser Ile Thr Glu Ile
20

(2) INFORMATION FOR SEQ ID NO:146:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:

Pro Leu Ser Ile Lys Tyr Leu Val Glu Leu Tyr His Leu Ser Met Ser
1 5 10 15

Gly Thr Lys Ile Ser Val Leu
20

(2) INFORMATION FOR SEQ ID NO:147:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:

Pro Gln Glu Leu Gly Asn Leu Arg Lys Leu Lys His Leu Asp Leu Gln
1 5 10 15

Arg Thr Gln Phe Leu Gln Thr Ile
20

(2) INFORMATION FOR SEQ ID NO:148:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:148:

Pro Arg Asp Ala Ile Cys Trp Leu Ser Lys Leu Glu Val Leu Asn Leu
1 5 10 15

Tyr Tyr Ser Tyr Ala Gly Trp Glu Leu Gln Ser Phe Gly Glu Asp Glu
20 25 30

Ala Glu Glu Leu Gly
35

(2) INFORMATION FOR SEQ ID NO:149:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:149:

Phe Ala Asp Leu Glu Tyr Leu Glu Asn Leu Thr Thr Leu Gly Ile Thr
1 5 10 15

Val Leu Ser Leu Glu Thr Leu Lys Thr
20 25

(2) INFORMATION FOR SEQ ID NO:150:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:150:

Leu Phe Glu Phe Gly Ala Leu His Lys His Ile Gln His Leu His Val
1 5 10 15

Glu Glu Cys Asn Glu Leu Leu Tyr Phe Asn Leu
20 25

(2) INFORMATION FOR SEQ ID NO:151:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:151:

Pro Ser Leu Thr Asn His Gly Arg Asn Leu Arg Arg Leu Ser Ile Lys
1 5 10 15

Ser Cys His Asp Leu Glu Tyr Leu Val Thr
20 25

(2) INFORMATION FOR SEQ ID NO:152:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:152:

Pro Ala Asp Phe Glu Asn Asp Trp Leu Pro Ser Leu Glu Val Leu Thr
1 5 10 15

Leu His Ser Leu His Asn Leu Thr Arg Val Trp Gly Asn
20 25

(2) INFORMATION FOR SEQ ID NO:153:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:153:

Ser Val Ser Gln Asp Cys Leu Arg Asn Ile Arg Cys Ile Asn Ile Ser
1 5 10 15

His Cys Asn Lys Leu Lys Asn Val Ser Trp Val Gln Lys Leu
20 25 30

(2) INFORMATION FOR SEQ ID NO:154:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:154:

Pro Lys Leu Glu Val Ile Glu Leu Phe Asp Cys Arg Glu Ile Glu Glu
1 5 10 15

Leu Ile Ser Glu His Glu Ser Pro Ser Val Glu Asp
20 25

(2) INFORMATION FOR SEQ ID NO:155:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:155:

Pro Thr Leu Phe Pro Ser Leu Lys Thr Leu Arg Thr Arg Asp Leu Pro
1 5 10 15

Glu Leu Asn Ser Ile Leu
20

(2) INFORMATION FOR SEQ ID NO:156:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:156:

Pro Ser Arg Phe Ser Phe Gln Lys Val Glu Thr Leu Val Ile Thr Asn
1 5 10 15

Cys Pro Arg Val Lys Lys Leu
20

(2) INFORMATION FOR SEQ ID NO:157:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5134 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:157:

AAGCTTTACA GATTGGATGA TCTCTTAATG CATGCTGAAG TGACTGCAAA AAGGTTAGCA 60

ATATTCAGTG GTTCTCGTTA TGAATATTTC ATGAACGGAA GCAGCACTGA GAAAATGAGG 120

CCCTTGTTAT CTGATTTTCT GCAAGAGATT GAGTCTGTCA AGGTAGAGTT CAGAAATGTT 180

TGCTTGCAAG TTCTGGATAT ATCACCTTTT TCCCTGACAG ATGGAGAAGG CCTTGTTAAT 240

TTCTTATTAA AAAACCAGGC CAAGGTGCCG AATGATGATG CTGTTTCTTC TGATGGAAGT 300

TTAGAGGATG CAAGCAGCAC TGAGAAAATG GGACTTCCAT CTGATTTTCT CCGAGAGATT 360

GAGTCTGTTG AGATAAAGGA GGCCAGAAAA TTATATGATC AAGTTTTGGA TGCAACACAT 420

TGTGAGACGA GTAAGCACGA TGGAAAAAGC TTTATCAACA TTATGTTAAC CCAACAGGAC 480

AAGGTGCTGG ACTATGATGC TGGTTCAGTG TCTTATCTTC TTAACCAAAT CTCAGTAGTT 540

AAAGACAAAA TATTGCACAT TGGCTCTTTA CTTGTAGATA TTGTACAGTA CCGGAATATG 600

CATATAGAAC TTACAGATCT CGCTGAACGT GTTCAAGATA AAAACTACAT TCGTTTCTTC 660

TCTGTCAAGG GTTATATTCC TGCTTGGTAT TACACACTAT ATCTCTCTGA TGTCAAGCAA 720

TTGCTTAAGT TTGTTGAGGC AGAGGTAAAG ATTATTTGTC TGAAAGTACC AGATTCTTCA 780

AGTTATAGCT TCCCTAAGAC AAATGGATTA GGATATCTCA ATTGCTTTTT AGGCAAATTG 840

GAGGAGCTTT TACGTTCTAA GCTCGATTTG ATAATCGACT TAAAACATCA GATTGAATCA 900

GTCAAGGAGG GCTTATTGTG CCTAAGATCA TTCATTGATC ATTTTTCAGA AAGCTATGTT 960

GAGCATGATG AAGCTTGTGG TCTTATAGCA AGAGTTTCTG TAATGGCATA CAAGGCTGAG 1020

TATGTCATTG ACTCATGCTT GGCCTATTCT CATCCACTCT GGTACAAAGT TCTTTGGATT 1080

TCTGAAGTTC TTGAGAATAT TAAGCTTGTA AATAAAGTTG TTGGGGAGAC ATGTGAAAGA 1140

AGGAACACTG AAGTTACTGT GCATGAAGTT GCAAAGACTA CCACTAATGT AGCACCATCT 1200

TTTTCAGCTT ATACTCAAAG AGCAAACGAA GAAATGGAGG GTTTTCAGGA TACAATAGAT 1260

GAATTAAAGG ATAAACTACT TGGAGGATCA CCTGAGCTTG ATGTCATCTC AATCGTTGGC 1320

ATGCCAGGAT TGGGCAAGAC TACACTAGCA AAGAAGATTT ACAATGATCC AGAAGTCACC 1380

TCTCGCTTCG ATGTCCATGC TCAATGTGTT GTGACTCAAT TATATTCATG GAGAGAGTTG 1440

TTGCTCACCA TTTTGAATGA TGTGCTTGAG CCTTCTGATC GCAATGAAAA AGAAGATGGA 1500

GAAATAGCTG ATGATCTACG CCGATTTTTG TTGACCAAGA GATTCTTGAT TCTCATTGAT 1560

GATGTGTGGG ACTATAAAGT GTGGGACAAT CTATGTATGT GCTTCAGTGA TGTTTCAAAT 1620

AGGAGTAGAA TTATCCTAAC AACCCGCTTG AATGATGTCG CCGAATATGT CAAATGTGAA 1680

AGTGATCCCC ATCATCTTCG TTTATTCAGA GATGACGAGA GTTGGACATT ATTACAGAAA 1740

GAAGTCTTTC AAGGAGAGAG CTGTCCACCT GAACTTGAAG ATGTGGGATT TGAAATATCA 1800

AAAAGTTGTA GAGGGTTGCC TCTCTCAGTT GTGTTAGTAG CTGGTGTTCT GAAACAGAAA 1860

AAGAAGACAC TAGATTCATG GAAAGTAGTA GAACAAAGTC TAAGTTCCCA GAGGATTGGC 1920

AGCTTGGAAG AGAGCATATC TATAATTGGA TTCAGTTACA AGAATTTACC ACACTATCTT 1980

AAGCCTTGTT TTCTCTATTT TGGAGGATTT TTGCAGGGAA AGGATATTCA TGACTCAAAA 2040

ATGACCAAGT TGTGGGTAGC TGAAGAGTTT GTACAAGCAA ACAACGAAAA AGGACAAGAA 2100

GATACCCGCA CAAGGTTTCT TGGACGATCT TATTGGTAGG AATCTGGTGA TGGCCATGGA 2160

GAAGAGACCT AATGCCAAGG TGAAAACGTG CCGCATTCAT GATTTGTTGC ATAAATTCTG 2220

CATGGAAAAG GCCAAACAAG AGGATTTCCT TCTCCAGATC AATAGGTAAA AAAAACTGTA 2280

TTAATTTTAC ATTACAAAAA AAAAGAACTG TATTAATTTT ACTGTATTAT GTTTATGCCA 2340

ACTCTCATTT CCATGTGTTC TCTTTTATTC AATTCAGTGG AGAAGGTGTA TTTCCTGAAC 2400

GATTGGAAGA ATACCGATTG TTCGTTCATT CTTACCAAGA TGAAATTGAT CTGTGGCGCC 2460

CATCTCGCTC TAATGTCCGC TCTTTACTAT TCAATGCAAT TGATCCAGAT AACTTGTTAT 2520

GGCCGCGTGA TATCTCCTTC ATTTTTGAGA GCTTCAAGCT TGTTAAAGTG TTGGATTTGG 2580

AATCATTCAA CATTGGTGGT ACTTTTCCCA TTGAAACACA ATATCTAATT CAGATGAAGT 2640

ACTTTGCGGC CCAAACTGAT GCAAATTCAA TTCCTTCATC TATAGCTAAG CTTGAAAATC 2700

TTGAGACTTT TGTCGTAAGA GGATTGGGAG GAGAGATGAT ATTACCTTGT TCACTTCTGA 2760

AGATGGTGAA ATTGAGGCAT ATACATGTAA ATGATCGGGT TTCTTTTGGT TTGCGTGAGA 2820

ACATGGATGT TTTAACTGGT AACTCACAAT AACCTAATTT GGAAACCTTT TCTACTCCGC 2880

GTCTCTTTTA TGGTAAAGAC GCAGAGAAGA TTTTGAGGAA GATGCCAAAA TTGAGAAAAT 2940

TGAGTTGCAT ATTTTCAGGG ACATTTGGTT ATTCAAGGAA ATTGAAGGGT AGGTGTGTTC 3000

GTTTTCCCAG ATTAGATTTT CTAAGTCACC TTGAGTCCCT CAAGCTGGTT TCGAACAGCT 3060

ATCCAGCCAA ACTTCCTCAC AAGTTCAATT TCCCCTCGCA ACTAAGGGAA CTGACTTTAT 3120

CAAAGTTCCG TCTACCTTGG ACCCAAATTT CGATCATTGC AGAACTGCCC AACTTGGTGA 3180

TTCTTAAGTT ATTGCTCAGA GCCTTTGAAG GGGATCACTG GGAAGTGAAA GATTCAGAGT 3240

TCCTAGAACT CAAATACTTA AAACTGGACA ACCTCAAAGT TGTACAATGG TCCATCTCTG 3300

ATGATGCTTT TCCTAAGCTT GAACATTTGG TTTTAACGAA ATGTAAGCAT CTTGAGAAAA 3360

TCCCTTCTCG TTTTGAAGAT GCTGTTTGTC TAAATAGAGT TGAGGTGAAC TGGTGCAACT 3420

GGAATGTTGC CAATTCAGCC CAAGATATTC AAACTATGCA ACATGAAGTT ATAGCAAATG 3480

ATTCATTCAC AGTTACTATA CAGCCTCCAG ATTGGTCTAA AGAACAGCCC CTTGACTCTT 3540

AGCAAAGGTT TGTTCTTGCT GTGTTCATCC AAGTGCATTT AACATTTATT CATTTTGTTT 3600

TACACCAGAA CATGTTTATT TTGCTAGTAT TACTTGATAC ATTAAAAGAA ATCGAACTCA 3660

TATTTCTGCT ACAGTCTTAA CTTTTCTTGG GCTTACTTGA GGTCTAGATT AGATCAATGG 3720

TTCATGTAAT TTTTAATTCA CTGTTTCATT CAACTGTCTT ATGATAGTTG TGAAATGACA 3780

ATATTGTTAT CCCTAGCCAA ATTTATTATG TTCAAATGAA AACTGATGTC ACAACTACTT 3840

TTTTGTGAAA TGTTTTTGAA TTTTTTGCTA TAAAATTGAC GAATTGACAG CTTCTATATT 3900

TGTCAGCTAA ACTCTTTGTC ACCAGAAGTG TATTTAGAAT TACTGTGGTT TTATGAAAGA 3960

GTTCTGTAGA ATTTTATGCT TTTGCAGAAT ATAGTTTAAA ACAACAACAC TTCTCTGTTT 4020

CAGAGATAGC AGAAGCTAAA GTTCAAGGCA TTTTGTTTAT TTCTAGAACA AGTGGAGTTC 4080

TTATGTTGAA TTCTTGAAAA GAAGAAGAAT CAGGAGCAGG TAAAGTTATC TCTTTTTATG 4140

TTTTTCTTCT TTTAGATGTT ATTTCTTCAT CTTGAACGTG AACACCGCTG AAAGCATTTT 4200

AATAAAACCG GAGAGAAAAA TAAGATCTTT TTATATAAAG CATTATCATG TAAATATGCC 4260

TAAATCCATA TGGTACAACT GTTTGACAAA ATGATAGAGA GGGGAGTTTT ATAGTATAAG 4320

TAAAACAGGA TTGAGAAAAA AATCCTTGCA CGATTTTCAA TTTCTGGCCA CATCACAATG 4380

TGTGTCAAAG TTCCCCTCTT TAAGTGGAAC AAGCAATCAG AAAAGCTCAT TCTTATCGGT 4440

GACATACCAA TACCAGCTGA CTGTCTCATC TTGGTTAACT TAGCCTTGCT TACTTAGACT 4500

ATTAGATTAG TTACTAATGA ACTGGTAAAT TGGAACCAAA TGTAGTTAGC TTGATGAGCT 4560

GGTAGACATG TATATATGAA GATACACGCG TAACTTTAGT CGATGGTTAA TTTTTCATTT 4620

TTGATTTTTT TTCTTCACAG AGTATATATG AACTTGGCCT AAAAGTTTTG CTTCACTAAT 4680

TTAACTATTA CCGTGGATGA AACAAGCATG GCAACATTTT CAACAACTAT CACTCAAGCA 4740

ATGTAAAAAA TGGAGGTTCT ACGAGCGGTA CATGTAAGAG TTTTGTGCAC ACAAGAGGTT 4800

CTGAGACTTG AACCATCCAT GTCCAAGGCA GTTGAGATGC TAGTAAAGAA AGAAGAAGAT 4860

GAGCCTGCAC TAATTAATCT CCCTGTATGA ATGAGAGAAT GAGAAAAAGA TGGAGCTTCA 4920

TGAACCAAAA GTTACCTTTT TTTTTTCTTC TTAATGGCAT TACTTTGAAG CACATGTTTG 4980

TTAGTTGTAA ATTGTAATGG TGAAGTGTTT GTAAATATAG GGAGTGATAT TTGAAAGAAT 5040

GGTTGTGTTA TCTTTACAAA CCGGAATCAT TTCTGTATAA TTTTCTTCTG TAATTTTTGG 5100

TTTCGGTTTA TTCATTACTC ATTTCAGTAA GCTT 5134

(2) INFORMATION FOR SEQ ID NO:158:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:158:

GGNATGGGNG GNNTNGGNAA RACNAC 26

(2) INFORMATION FOR SEQ ID NO:159:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:159:

NCGNGWNGTN AKDAWNCGNA 20

(2) INFORMATION FOR SEQ ID NO:160:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:160:

GGWNTBGGWA ARACHAC 17

(2) INFORMATION FOR SEQ ID NO:161:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:161:

NRYNRDNGTN GTYTTNCCNA NNCCNNSNRK NCC 33

(2) INFORMATION FOR SEQ ID NO:162:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:162:

GGNMYNSSNG GNNTNGGNAA RACNAC 26

(2) INFORMATION FOR SEQ ID NO:163:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:163:

TYGAYGAYRT BRA 13

(2) INFORMATION FOR SEQ ID NO:164:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:164:

TYCCAVAYRT CRTCNA 16

(2) INFORMATION FOR SEQ ID NO:165:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:165:

VYMNAYRTCR TCNADNAVNA NNARNA 26

(2) INFORMATION FOR SEQ ID NO:166:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:166:

WWNMRRDTNY TNNTNBTNHT NNARNA 26

(2) INFORMATION FOR SEQ ID NO:167:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:167:

NCGNGWNGTN AKDWNCGNGA 20

(2) INFORMATION FOR SEQ ID NO:168:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:168:

NCKNSWNGTN ADDATDAATN G 21

(2) INFORMATION FOR SEQ ID NO:169:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:169:

NARNGGNARN CC 12

(2) INFORMATION FOR SEQ ID NO:170:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:170:

GGWYTBCCWY TBGCHYT 17

(2) INFORMATION FOR SEQ ID NO:171:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:171:

ARDGCVARWG GVARNCC 17

(2) INFORMATION FOR SEQ ID NO:172:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:172:

NRNNWYNAVN SHNARNGGNA RNCC 24

(2) INFORMATION FOR SEQ ID NO:173:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:173:

GGNYTNCCNY TNDSNBT 17

(2) INFORMATION FOR SEQ ID NO:174:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:174:

ARRTTRTCRT ADSWRAWYTT 20

(2) INFORMATION FOR SEQ ID NO:175:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:175:

ARNYYNTYRT ANSRNANNYY 20

(2) INFORMATION FOR SEQ ID NO:176:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:176:

RRNWTHWSNT AYRANRVNY 19

(2) INFORMATION FOR SEQ ID NO:177:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:177:

GTNTTYYTNW SNTTYMGRGG 20

(2) INFORMATION FOR SEQ ID NO:178:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:178:

CCNATHTTYT AYRWBGTNGA YCC 23

(2) INFORMATION FOR SEQ ID NO:179:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:179:

GTNGGNATHG AYRMNCA 17

(2) INFORMATION FOR SEQ ID NO:180:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:180:

RAARCANGCD ATRTCNARRA A 21

(2) INFORMATION FOR SEQ ID NO:181:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:181:

TTYYTNGAYA THGCNTGYTT 20

(2) INFORMATION FOR SEQ ID NO:182:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:182:

CCCARTCYYK NADNWRRTCR TGCAT 25

(2) INFORMATION FOR SEQ ID NO:183:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:183:

ATGCAYGAYY WNHTNMRRGA YATGGG 26

(2) INFORMATION FOR SEQ ID NO:184:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:184:

NARNSWYTYN ARYTT 15

(2) INFORMATION FOR SEQ ID NO:185:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:185:

WSNAARYTNR ARWSNYT 17

(2) INFORMATION FOR SEQ ID NO:186:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:186:

DWWYTCNARN SWNYKNARNC C 21

(2) INFORMATION FOR SEQ ID NO:187:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:187:

GGNYTNMRNW NNYTNGA 17

(2) INFORMATION FOR SEQ ID NO:188

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:188:

Leu Lys Phe Ser Tyr Asp Asn Leu Glu Ser Asp Leu Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:189:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:189:

Gly Val Tyr Gly Pro Gly Gly Val Gly Lys Thr Thr Leu Met Gln Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:190:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:190:

Gly Gly Leu Pro Leu Ala Leu Ile Thr Leu Gly Gly Ala Met

(2) INFORMATION FOR SEQ ID NO:191:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION: /note= "Xaa is Met or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 3
(D) OTHER INFORMATION: /note= "Xaa is Gly or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION: /note= "Xaa is Ile, Leu or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(D) OTHER INFORMATION: /note= "Xaa is Ile, Leu or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 11
(D) OTHER INFORMATION: /note= "Xaa is Ala or Met"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:191:

```
Gly Xaa Xaa Gly Xaa Gly Lys Thr Thr Xaa Xaa
1               5                  10
```

(2) INFORMATION FOR SEQ ID NO:192:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Xaa is Phe or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION: /note= "Xaa is Arg or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 3
(D) OTHER INFORMATION: /note= "Xaa is Ile, Val or Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION: /note= "Xaa is Ile, Leu or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /note= "Xaa is Ile or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 7
(D) OTHER INFORMATION: /note= "Xaa is Ile or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(D) OTHER INFORMATION: /note= "Xaa is Ile, Leu or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 11
(D) OTHER INFORMATION: /note= "Xaa is Asp or Trp"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:192:

Xaa Xaa Xaa Leu Xaa Xaa Xaa Asp Asp Xaa Xaa
1 5 10

(2) INFORMATION FOR SEQ ID NO:193:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Xaa is Ser or Cys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION: /note= "Xaa is Arg or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 3
(D) OTHER INFORMATION: /note= "Xaa is Phe, Ile or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 4
(D) OTHER INFORMATION: /note= "Xaa is Ile or Met"

(ix) FEATURE:

(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION: /note= "Xaa is Ile, Leu or Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 7
(D) OTHER INFORMATION: /note= "Xaa is Ser, Cys or Thr"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:193:

Xaa Xaa Xaa Xaa Xaa Thr Xaa Arg
1 5

(2) INFORMATION FOR SEQ ID NO:194:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION: /note= "Xaa is Thr, Ala or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /note= "Xaa is Leu or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 7
(D) OTHER INFORMATION: /note= "Xaa is Ile, Val or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 8
(D) OTHER INFORMATION: /note= "Xaa is Val or Thr"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:194:

Gly Leu Pro Leu Xaa Xaa Xaa Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:195:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Xaa is Lys or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION: /note= "Xaa is Ile or Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION: /note= "Xaa is Asp or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /note= "Xaa is Ala, Gly or Asn"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:195:

Xaa Xaa Ser Tyr Xaa Xaa Leu
1 5

(2) INFORMATION FOR SEQ ID NO:196:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:196:

Asn Ser His Arg
1

(2) INFORMATION FOR SEQ ID NO:197:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:197:

Arg Asp Arg Arg Arg Val Asp Pro Cys
1 5

(2) INFORMATION FOR SEQ ID NO:198:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:198:

Thr Gly Asp Leu
1

(2) INFORMATION FOR SEQ ID NO:199:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:199:

His Gly Thr Tyr
1

(2) INFORMATION FOR SEQ ID NO:200:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:200:

Arg Met Ser His Gly Phe Arg Asn Ser Gln Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:201:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:201:

Gly Glu Met Val Glu Ser Thr Gly Lys Arg Ser Thr Lys Arg Arg Ala
1 5 10 15

Leu Leu Phe Thr Ala Leu Cys Ser Lys Leu Ile
20 25

Claims

1. A substantially pure oligonucleotide comprising the sequence:

5′ GGNATGGGNGGNNTNGGNAARACNAC 3′, [SEQ. ID NO:158] wherein N is A, T, G, or C; and R is A or G.

2. A substantially pure oligonucleotide comprising the sequence:

5′ NARNGGNARNCC 3′, [SEQ. ID NO: 169] wherein N is A, T, G or C; and R is A or G.

3. A substantially pure oligonucleotide comprising the sequence:

5′NCGNGWNGTNAKDAWNCGNGA 3′, [SEQ. ID NO: 159] wherein N is A, T, G or C; W is A or T; D is A, G, or T; and K is G or T.

4. A substantially pure oligonucleotide comprising the sequence:

5′ GGWNTBGGWAARACHAC 3′, [SEQ ID NO: 160] wherein N is A, T, G or C; R is G or A; B is C, G, or T; H is A, C, or T; and W is A or T.

5. A substantially pure oligonucleotide comprising the sequence:

5′ TYGAYGAYRTBKRBRA 3′, [SEQ. ID NO: 163] wherein R is G or A; B is C, G, or T; D is A, G, or T; Y is T or C; and K is G or T.

6. A substantially pure oligonucleotide comprising the sequence:

5′ TYCCAVAYRTCRTCNA 3′, [SEQ ID NO: 164] wherein N is A, T, G or C; R is G or A; V is G or C or A; and Y is T or C.

7. A substantially pure oligonucleotide comprising the sequence:

5′ GGWYTBCCWYTBGCHYT 3′, [SEQ ID NO.: 170] wherein B is C, G, or T; H is A, C, or T; W is A or T; and Y is T or C.

8. A substantially pure oligonucleotide comprising the sequence:

5′ ARDGCVARWGGVARNCC 3′, [SEQ ID NO: 171] wherein N is A, T, G or C; R is G or A; W is A or T; D is A, G, or T; and V is G, C, or A.

9. A substantially pure oligonucleotide comprising the sequence:

5′ ARRTTRTCRTADSWRAWYTT 3′, [SEQ ID NO: 174] wherein R is G or A; W is A or T; D is A, G, or T; S is G or C; and Y is C or T.

10. A recombinant plant gene comprising the DNA sequence:

5′ GGNATGGGNGGNNTNGGNAARACNAC 3′, [SEQ ID NO: 158] wherein N is A, T, G or C; and R is A or G.

11. The gene of claim 10, further comprising the sequence:

5′ NARNGGNARNCC 3′, [SEQ ID NO: 169] wherein N is A, T, G or C; and R is A or G.

12. The gene of claim 11, further comprising the sequence:

5′ NCGNGWNGTNAKDAWNCGNGA 3′, [SEQ ID NO: 167] wherein N is A, T, G or C; W is A or T; D is A, G or T; and K is G or T.

13. A recombinant plant gene comprising a combination of any two or more sequences of claims 10, 11 and 12.

14. A substantially pure plant polypeptide comprising the amino acid sequence:

Gly Xaa_1 Xaa_2 Gly Xaa_3 Gly Lys Thr Thr Xaa_4 Xaa_5, [SEQ ID NO: 191], wherein Xaa_1 is Met or Pro; Xaa_2 is Gly or Pro; Xaa_3 is Ile, Leu, or Val; Xaa_4 is Ile, Leu, or Thr; and Xaa_5 is Ala or Met.

15. A substantially pure plant polypeptide comprising the amino acid sequence:

Xaa_1 Xaa_2 Xaa_3 Leu Xaa_4 Xaa_5 Xaa_6 Asp Asp Xaa_7 Xaa_8, [SEQ ID NO: 192],
wherein Xaa_1 is Phe or Lys; Xaa_2 is Arg or Lys; Xaa_3 is Ile, Val, or Phe; Xaa_4 is Ile, Leu, or Val; Xaa_5 is Ile or Leu; Xaa_6 is Ile or Val; Xaa_7 is Ile, Leu, or Val; and Xaa_8 is Asp or Trp.

16. A substantially pure plant polypeptide comprising the amino acid sequence:

Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Thr Xaa_6 Arg, [SEQ ID NO: 193]
wherein Xaa_1 is Ser or Cys; Xaa_2 is Arg or Lys; Xaa_3 is Phe, Ile, or Val; Xaa_4 is Ile, or Met; Xaa_5 is Ile, Leu, or Phe; Xaa_6 is Ser, Cys, or Thr.

17. A substantially pure plant polypeptide comprising the amino acid sequence:

Gly Leu Pro Leu Xaa_1 Xaa_2 Xaa_3 Xaa_4, [SEQ ID NO: 194],
wherein Xaa_1 is Thr, Ala, or Ser; Xaa_2 is Leu or Val; Xaa_3 is Ile, Val, or Lys; and Xaa_4 is Val or Thr.

18. A substantially pure plant polypeptide comprising the amino acid sequence:

Xaa_1 Xaa_2 Ser Tyr Xaa_3 Xaa_4 Leu, {SEQ ID NO: 195], wherein Xaa_1 is Lys or Gly; Xaa_2 is Ile or Phe; Xaa_3 is Asp or Lys; and Xaa_4 is Ala, Gly, or Asn.

19. A method of isolating a disease-resistance gene or fragment thereof from a plant cell, comprising:

(a) providing a sample of plant cell DNA;

(b) providing a pair of oligonucleotides having sequence homology to a conserved region of an RPS disease-resistance gene;

(c) combining said pair of oligonucleotides with said plant cell DNA sample under conditions suitable for polymerase chain reaction-mediated DNA amplification; and

(d) isolating said amplified disease-resistance gene or fragment thereof.

20. The method of claim 19, wherein said amplification is carried out using a reverse-transcription polymerase chain reaction.

21. The method of claim 19, wherein said reverse-transcription polymerase chain reaction is RACE.

22. A method of identifying a plant disease-resistance gene in a plant cell, comprising:

(a) providing a preparation of plant cell DNA;

(b) providing a detectably-labelled DNA sequence having homology to a conserved region of an RPS gene;

(c) contacting said preparation of plant cell DNA with said detectablly-labelled DNA sequence under hybridization conditions providing detection of genes having 50% or greater sequence identity; and

(d) identifying a disease-resistance gene by its association with said detectable label.

23. The method of claim 22, wherein said DNA sequence is produced according to the method of claim 19.

24. The method of claim 22, wherein said preparation of plant cell DNA is isolated from a plant genome.

25. A method of isolating a disease-resistance gene from a recombinant plant cell library, comprising:

(a) providing a recombinant plant cell library;

(b) contacting said recombinant plant cell library with a detectably-labelled gene fragment produced according to the method of claim 19 under hybridization conditions providing detection of genes having 50% or greater sequence identity; and

(c) isolating a member of a disease-resistance gene by its association with said detectable label.

26. A method of isolating a disease-resistance gene from a recombinant plant cell library, comprising:

(a) providing a recombinant plant cell library;

(b) contacting said recombinant plant cell library with a detectably-labelled oligonucleotide of any of claims 1-9 under hybridization conditions providing detection of genes having 50% or greater sequence identity; and

(c) isolating a disease-resistance gene by its association with said detectable label.

27. A recombinant plant polypeptide capable of conferring disease-resistance wherein said plant polypeptide comprises a P-loop domain or nucleotide binding site domain.

28. The recombinant plant polypeptide of claim 27, wherein said polypeptide further comprises a leucine-rich repeating domain.

29. A recombinant plant polypeptide capable of conferring disease-resistance wherein said plant polypeptide contains a leucine-rich repeating domain.

30. A plant disease-resistance gene isolated according to the method comprising:

(a) providing a sample of plant cell DNA;

(b) providing a pair of oligonucleotides having sequence homology to a conserved region of an RPS disease-resistance gene;

(c) combining said pair of oligonucleotides with said plant cell DNA sample under conditions suitable for polymerase chain reaction-mediated DNA amplification; and

(d) isolating said amplified disease-resistance gene or fragment thereof.

31. A plant disease-resistance gene isolated according to the method comprising:

(a) providing a preparation of plant cell DNA;

(b) providing a detectably-labelled DNA sequence having homology to a conserved region of an RPS gene;

(c) contacting said preparation of plant cell DNA with said detectably-labelled DNA sequence under hybridization conditions providing detection of genes having 50% or greater sequence identity; and

(d) identifying a disease-resistance gene by its association with said detectable label.

32. A plant disease-resistance gene according to the method comprising:

(a) providing a recombinant plant cell library;

(b) contacting said recombinant plant cell library with a detectably-labelled gene fragment produced according to the method of claims 1-4 under hybridization conditions providing detection of genes having 50% or greater sequence identity; and

(c) isolating a disease-resistance gene by its association with said detectable label.

33. A method of identifying a plant disease-resistance gene comprising:

(a) providing a plant tissue sample;

(b) introducing by biolistic transformation into said plant tissue sample a candidate plant disease-resistance gene;

(c) expressing said candidate plant disease-resistance gene within said plant tissue sample; and

(d) determining whether said plant tissue sample exhibits a disease-resistance response, whereby a response identifies a plant disease-resistance gene.

34. The method of claim 33, wherein said plant tissue sample comprises leaf, root, flower, fruit, or stem tissue.

35. The method of claim 33, wherein said candidate plant disease-resistance gene is obtained from a cDNA expression library.

36. The method of claim 33, wherein said disease-resistance response is the hypersensitive response.

37. A plant disease-resistance gene isolated according to the method comprising:

(a) providing a plant tissue sample;

(b) introducing by biolistic transformation into said plant tissue sample a candidate plant disease-resistance gene;

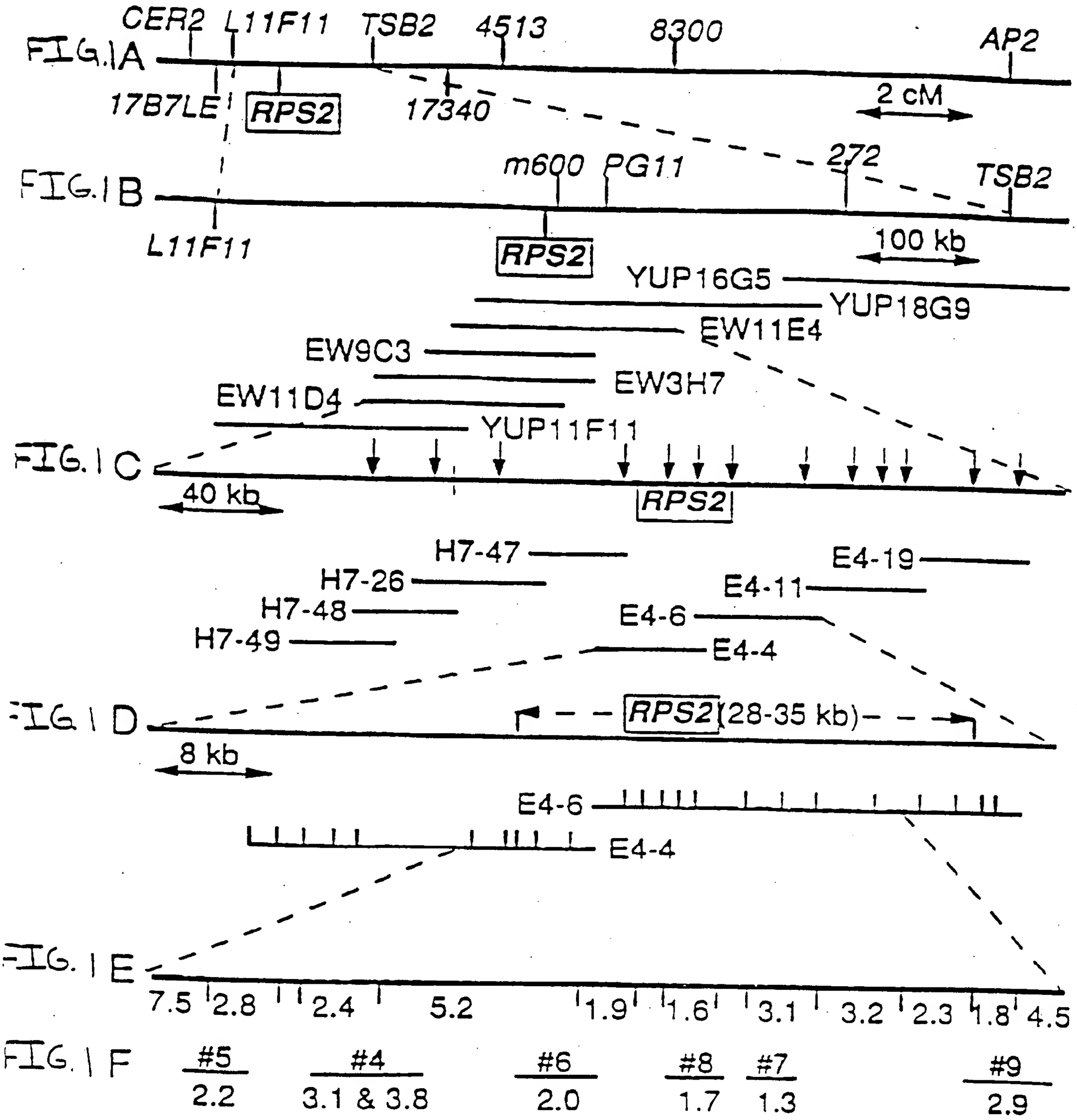
(c) expressing said candidate plant disease-resistance gene within said plant tissue sample; and

(d) determining whether said plant tissue sample exhibits a disease-resistance response, whereby a response identifies a plant disease-resistance gene.

38. A purified antibody which binds specifically to an rps family protein.

39. A DNA sequence substantially identical to the DNA sequence shown in Figure 12.

40. A substantially pure polypeptide having a sequence substantially identical to a Prf amino acid sequence shown in Figure 5 (A or B).


CER2
L11F11
TSB2
4513
8300
AP2
FIG.1A
17B7LE
RPS2
17340
2 cM
m600
PG11
272
TSB2
FIG.1B
L11F11
RPS2
100 kb
YUP16G5
YUP18G9
EW11E4
EW9C3
EW3H7
EW11D4
YUP11F11
FIG.1C
40 kb
RPS2
H7-47
E4-19
H7-26
E4-11
H7-48
E4-6
H7-49
E4-4
FIG.1D
RPS2 (28-35 kb)
8 kb
E4-6
E4-4
FIG.1E
7.5
2.8
2.4
5.2
1.9
1.6
3.1
3.2
2.3
1.8
4.5
FIG.1F
#5
2.2
#4
3.1 & 3.8
#6
2.0
#8
1.7
#7
1.3
#9
2.9

```
                AAGTAAAAGAAAGAGCGAGAAATCATCGAAATCGATTTCATCTCATCTCTTATCGTTGGC
          1     ------------+-----------+-----------+-----------+-----------+ 60
                TTCATTTTCTTTCTCGCTCTTTAGTAGCTTTAGCTAAAGTAGAGTAGAGAATAGCAACCG

a               K  *  K  K  E  R  E  I  I  E  M  D  F  I  S  S  L  I  V  C  -
b                S  K  R  X  S  E  R  S  S  K  W  I  S  S  H  L  L  S  L  A  -
c                 V  K  E  R  A  R  N  H  R  N  G  F  H  L  I  S  Y  R  W  L  -

                TGTGCTCAGGTGTTGTGTCAATCTATGAATATGGCGGAGAAGAGGACATAAGACTGAT
         61     ------------+-----------+-----------+-----------+-----------+ 120
                ACACGAGTCCACAACACACTTAGATACTTATACCGCCTCTCTTCTCCTGTATTCTGACTA

a               C  A  Q  V  L  C  E  S  M  N  M  A  E  R  R  G  H  K  T  D  -
b                V  L  R  C  C  V  N  L  *  I  W  R  R  E  E  D  I  R  L  I  -
c                 C  S  G  V  V  *  I  Y  E  Y  G  G  E  R  R  T  *  D  *  S  -

                CTTAGACAAGCCATCACTGATCTTCAAACAGCCATCCGTGACTTCAAGGCCATACCTGAT
        121     ------------+-----------+-----------+-----------+-----------+ 180
                GAATCTGTTCGGTAGTGACTAGAACTTTGTCGGTAGCCACTGAACTTCCGGTATGGACTA

a               L  R  Q  A  I  T  D  L  E  T  A  I  G  D  L  R  A  I  R  D  -
b                L  D  K  P  S  L  I  L  K  Q  P  S  V  T  *  R  P  Y  V  M  -
c                 *  T  S  H  H  *  S  *  N  S  H  R  *  L  E  C  H  T  *  *  -

                GACCTGACTTTACGGATCCAACAAGACGGTCTAGAGGGACGAAGCTGCTCAAATCCTGCC
        181     ------------+-----------+-----------+-----------+-----------+ 240
                CTGGACTGAAATGCCTAGGTTGTTCTGCCAGATCTCCCTGCTTCGACGACTTTAGCACGG

a               D  L  T  L  R  I  Q  Q  D  G  L  E  G  R  S  C  S  N  R  A  -
b                T  *  L  Y  G  S  N  K  T  V  *  R  D  E  A  A  Q  I  V  P  -
c                 P  D  F  T  D  P  T  R  R  S  R  G  T  K  L  L  K  S  C  Q  -

                AGAGAGTGGCTTAGTGCGGTGCAAGTAACGGAGACTAAAACAGCCCTACTTTTACTGAGG
        241     ------------+-----------+-----------+-----------+-----------+ 300
                TCTCTCACCGAATCACGCCACGTTCATTGCCTCTGATTTTGTCGGGATGAAAATCACTCC

a               R  E  W  L  S  A  V  Q  V  T  E  T  K  T  A  L  L  L  V  R  -
b                E  S  G  L  V  R  C  K  *  R  R  L  K  Q  P  Y  F  *  *  G  -
c                 R  V  A  *  C  G  A  S  N  G  D  *  N  S  P  T  F  S  E  V  -

                TTTAGGCGTCGGGAACAGAGGACGCGAATGAGGAGGAGATACCTCAGTTGTTTCGGTTGT
        301     ------------+-----------+-----------+-----------+-----------+ 360
                AAATCCGCAGCCCTTGTCTCCTGCGCTTACTCCTCCTCTATGGAGTCAACAAAGCCAACA

a               F  R  R  R  E  Q  R  T  R  M  R  R  R  Y  L  S  C  F  G  C  -
b                L  G  V  G  N  R  G  R  E  *  G  G  D  T  S  V  V  S  V  V  -
c                 *  A  S  G  T  E  D  A  N  E  E  E  I  P  Q  L  F  R  L  C  -

                GCCGACTACAAACTGTCCAACGAAGGTTTCTGCCATATTGAAGAGCATTGGTGAGCTGAG
```

FIGURE 2

```
        361 ----------+----------+----------+----------+----------+----------+---------- 420
            CGGCTGATGTTTGACACGTTCTTCCAAAGACGGTATAACTTCTCGTAACCACTCGACTCT

a           A  D  Y  K  L  C  K  K  V  S  A  I  L  K  S  I  G  E  L  R  -
b            P  T  T  N  C  A  R  R  F  L  P  Y  *  R  A  L  V  S  *  E  -
c             R  L  Q  T  V  Q  E  G  F  C  H  I  E  E  H  W  *  A  E  R  -

            GAACGCTCTGAAGCTATCAAAACAGATGGCGGGTCAATTCAAGTAACTTCTAGAGACATA
        421 ----------+----------+----------+----------+----------+----------+---------- 480
            CTTGCGAGACTTCGATAGTTTTGTCTACCGCCCAGTTAAGTTCATTGAACATCTCTCTAT

a           E  R  S  E  A  I  K  T  D  G  G  S  I  Q  V  T  =  R  E  I  -
b            N  A  L  K  L  S  K  Q  M  A  G  Q  F  K  *  L  V  E  R  Y  -
c             T  L  *  S  Y  Q  N  R  W  R  V  N  S  S  N  L  *  R  D  T  -

            CCCATCAAGTCCGTTGTCGGAAATACCACGATGATGGAACAGGTTTTGGAATTTCTCAGT
        481 ----------+----------+----------+----------+----------+----------+---------- 540
            GGGTAGTTCAGGCAACAGCCTTTATGGTGCTACTACCTTGTCCAAAACCTTAAAGAGTCA

a           P  I  K  S  V  V  G  N  T  T  M  M  Z  Q  V  L  E  F  L  S  -
b            P  S  S  P  L  S  E  I  P  R  *  W  N  R  F  W  N  F  S  V  -
c             H  Q  V  R  C  R  K  Y  H  D  D  G  T  G  F  G  I  S  Q  *  -

            GAAGAAGAAGAAAGAGGAATCATTGGTGTTTATGGACCTCGTGGGGTTGGCAAGACAACC
        541 ----------+----------+----------+----------+----------+----------+---------- 600
            CTTCTTCTTCTTTCTCCTTAGTAACCACAAATACCTGGACCACCCCAACCCTTCTGTTGG

a           E  E  E  E  R  G  I  I  G  V  Y  G  P  G  G  V  G  K  T  T  -
b            K  K  K  K  E  E  S  L  V  F  M  D  L  V  G  L  G  R  Q  R  -
c             R  R  R  K  R  N  H  W  C  L  W  T  W  W  C  W  E  D  N  V  -

            TTAATGCAGAGCATTAACAACGAGCTGATCACAAAAGGACATCACTATGATGTACTGATT
        601 ----------+----------+----------+----------+----------+----------+---------- 660
            AATTACGTCTCGTAATTGTTGCTCGACTAGTGTTTTCCTGTAGTCATACTACATGACTAA

a           L  M  Q  S  I  N  N  E  L  I  T  K  G  H  Q  Y  D  V  L  I  -
b            *  C  R  A  L  T  T  S  *  S  Q  K  D  I  S  M  M  Y  *  F  -
c             N  A  E  H  *  Q  R  A  D  H  K  R  T  S  V  *  C  T  D  L  -

            TGGGTTCAAATGTCCAGAGAATTCGGCGAGTGTACAATTCAGCAAGCCGTTGGAGCACGG
        661 ----------+----------+----------+----------+----------+----------+---------- 720
            ACCCAAGTTTACAGGTCTCTTAAGCCGCTCACATGTTAAGTCGTTCGGCAACCTCGTGCC

a           W  V  Q  M  S  R  E  F  G  E  C  T  I  Q  Q  A  V  G  A  R  -
b            G  F  R  C  P  E  N  S  A  S  V  Q  F  S  K  P  L  E  R  G  -
c             G  S  N  V  Q  R  I  R  R  V  Y  N  S  A  S  R  W  S  T  V  -

            TTGGGTTTATCTTGGGACGAGAAGGAGACCGGCGAAAACAGAGCTTTCAAGATATACAGA
        721 ----------+----------+----------+----------+----------+----------+---------- 780
            AACCCAAATAGAACCCTGCTCTTCCTCTGGCCGCTTTTGTCTCGAAAGTTCTATATGTCT

a           L  G  L  S  W  D  E  R  E  T  G  E  N  R  A  L  K  I  Y  R  -
b            W  V  Y  L  G  T  R  R  R  P  A  K  T  E  L  *  R  Y  T  E  -
c             G  F  I  L  G  R  E  G  D  R  R  K  Q  S  F  E  D  I  Q  S  -

            GCTTTGAGACAGAAACGTTTCTTGTTGTTGCTAGATGATGTCTGGGAAGAGATAGACTTC
        781 ----------+----------+----------+----------+----------+----------+---------- 840
            CGAAACTCTGTCTTTGCAAAGAACAACAACGATCTACTACAGACCCTTCTCTATCTGAAG

a           A  L  R  Q  K  R  F  L  L  L  L  D  D  V  W  E  E  I  D  L  -
b            L  *  D  R  N  V  S  C  C  C  *  M  M  S  G  K  R  *  T  W  -
c             F  E  T  E  T  F  L  V  V  A  R  *  C  L  G  R  D  R  L  C  -
```

FIG. 2 CONTINUED

```
                GAGAAAACTGGAGTTCCTCGACCTGACAGGGAAAACAAATGCAAGGTGATGTTCAGGACA
          841   ----------+---------+---------+---------+---------+---------- 900
                CTCTTTTGACCTCAAGGAGCTGGACTGTCCCTTTTGTTTACGTTCCACTACAAGTGCTGT

a                E  K  T  G  V  P  R  P  D  R  E  N  K  C  K  V  M  F  T  T  -
b                 R  K  L  E  F  L  D  L  T  G  K  T  N  A  R  *  C  S  R  H  -
c                  E  N  W  S  S  S  S  T  *  Q  G  K  Q  M  Q  G  D  V  H  D  T  -

                CGGTCTATAGCATTATGCAACAATATGGGTGCGGAATACAAGTTGAGAGTGGAGTTTCTC
          901   ----------+---------+---------+---------+---------+---------- 960
                GCCAGATATCGTAATACGTTGTTATACCCACGCCTTATGTTCAACTCTCACCTCAAAGAG

a                R  S  I  A  L  C  N  N  M  G  A  E  Y  K  L  R  V  E  F  L  -
b                 G  L  *  H  Y  A  T  I  W  V  R  N  T  S  *  E  W  S  F  W  -
c                  V  Y  S  I  M  Q  Q  Y  G  C  G  I  Q  V  E  S  G  V  S  G  -

                GAGAAGAAACACGCGTGGGAGCTGTTCTCTAGTAAGGTATGGAGAAAAGATCTTTTAGAG
          961   ----------+---------+---------+---------+---------+---------- 1020
                CTCTTCTTTGTGCGCACCCTCGACAAGACATCATTCCATACCTCTTTTCTAGAAAATCTC

a                E  K  K  H  A  W  E  L  F  C  S  K  V  W  R  K  D  L  L  E  -
b                 R  R  N  T  R  G  S  C  S  V  V  R  Y  G  E  K  I  F  *  S  -
c                  E  E  T  R  V  G  A  V  L  *  *  G  M  E  R  R  S  F  R  V  -

                TCATCATCAATTCGCCGGCTCCCGAGATTATAGTGAGTAAATGTCGAGGATTGCCACTA
         1021   ----------+---------+---------+---------+---------+---------- 1080
                AGTAGTAGTTAAGCGGCCGAGCGGCCTCTAATATCACTCATTTACAGCTCCTAACGGTGAT

a                S  S  S  I  R  R  L  A  E  I  I  V  S  K  C  G  G  L  P  L  -
b                 H  H  Q  F  A  G  S  R  R  L  *  *  V  N  V  E  D  C  R  *  -
c                  I  I  N  S  P  A  R  G  D  Y  S  E  *  M  W  R  I  A  T  S  -

                GCGTTGATCACTTTAGGAGGAGCCATGGCTCATAGAGAGACAGAAGAAGAGTGGATCCAT
         1081   ----------+---------+---------+---------+---------+---------- 1140
                CGCAACTAGTGAAATCCTCCTCGGTACCGAGTATCTCTCTGTCTTCTTCTCACCTAGGTA

a                A  L  I  T  L  G  G  A  M  A  H  R  E  T  E  E  E  W  I  H  -
b                 R  *  S  L  *  E  E  P  W  L  I  E  R  Q  R  K  S  G  S  M  -
c                  V  D  H  F  R  R  S  H  G  S  *  R  D  R  R  E  V  D  P  C  -

                GCTAGTGAACTTCTGACTAGATTTCCAGCAGAGATCAAGGGTATGAACTATGTATTTGCC
         1141   ----------+---------+---------+---------+---------+---------- 1200
                CGATCACTTCAAGACTGATCTAAAGGTCGTCTCTACTTCCCATACTTCATACATAAACGG

a                A  S  E  V  L  T  R  F  P  A  E  M  R  G  M  N  Y  V  F  A  -
b                 L  V  K  P  *  L  D  F  Q  Q  R  *  R  V  *  T  M  Y  L  P  -
c                  *  *  S  S  D  *  I  S  S  R  D  E  G  Y  E  L  C  I  C  P  -

                CTTTTCAAATTCAGCTACGACAACCTCGAGAGTGATCTGCTTCGGTCTTGTTTCTTGTAC
         1201   ----------+---------+---------+---------+---------+---------- 1260
                GAAAACTTTAAGTCGATGCTGTTGGAGCTCTCACTAGACGAAGCCAGAACAAAGAACATG

a                L  L  K  F  S  Y  D  N  L  E  S  D  L  L  R  S  C  P  L  Y  -
b                 F  *  N  S  A  T  T  T  S  R  V  I  C  F  G  L  V  S  C  T  -
c                  F  E  I  Q  L  R  Q  P  R  E  *  S  A  S  V  L  F  L  V  L  -

                TGCGCTTTATTCCCAGAAGAACATTCTATAGAGATCGAGCAGCTTGTTGAGTACTGGGTC
         1261   ----------+---------+---------+---------+---------+---------- 1320
                ACGCGAAATAAGGGTCTTCTTGTAAGATATCTCTAGCTCGTCGAACAACTCATGACCCAG

a                C  A  L  F  P  E  E  H  S  I  E  I  E  Q  L  V  E  Y  W  V  -
```

FIG. 2 CONTINUED

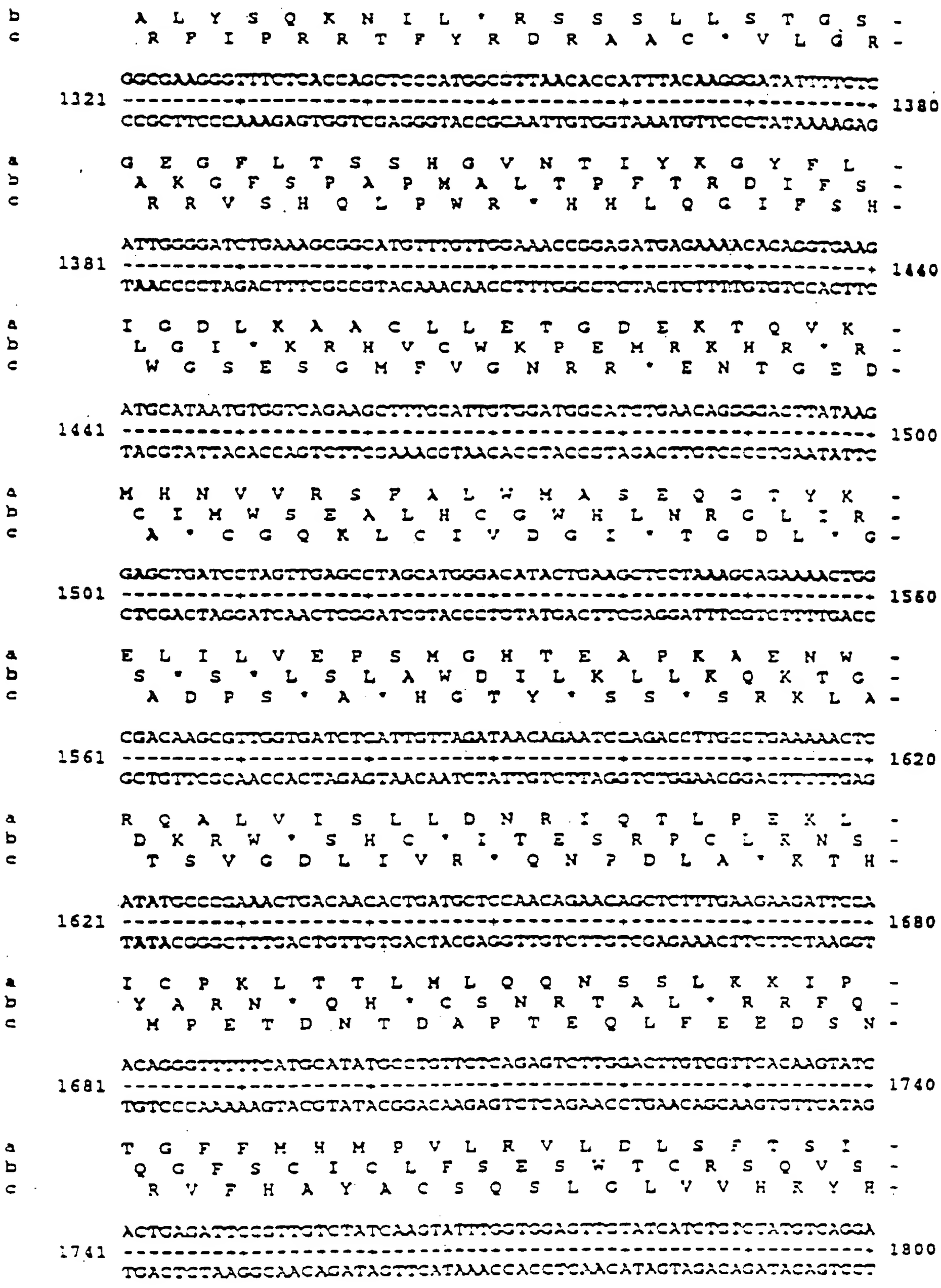


FIG. 2 CONTINUED

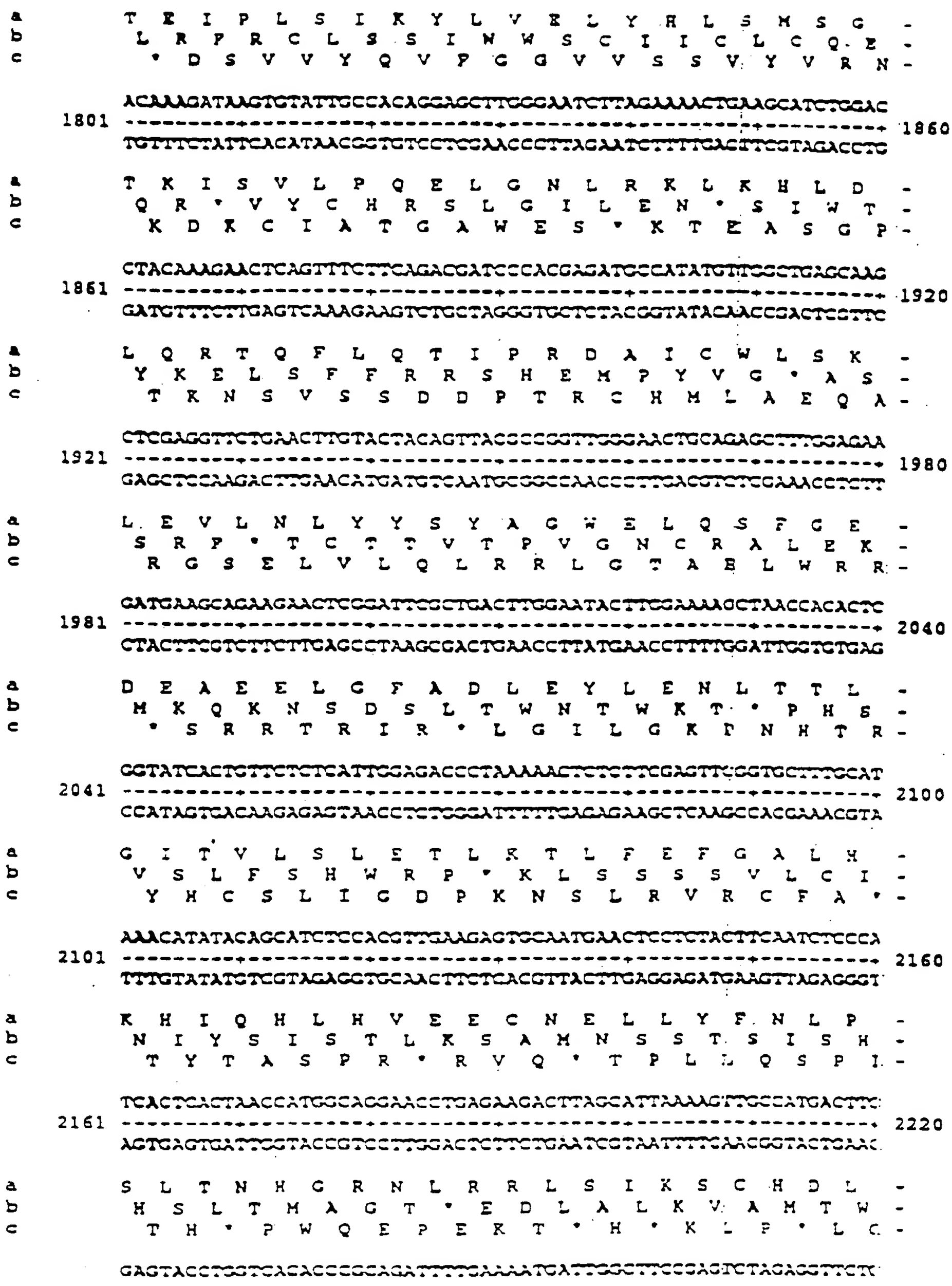


FIG. 2 CONTINUED

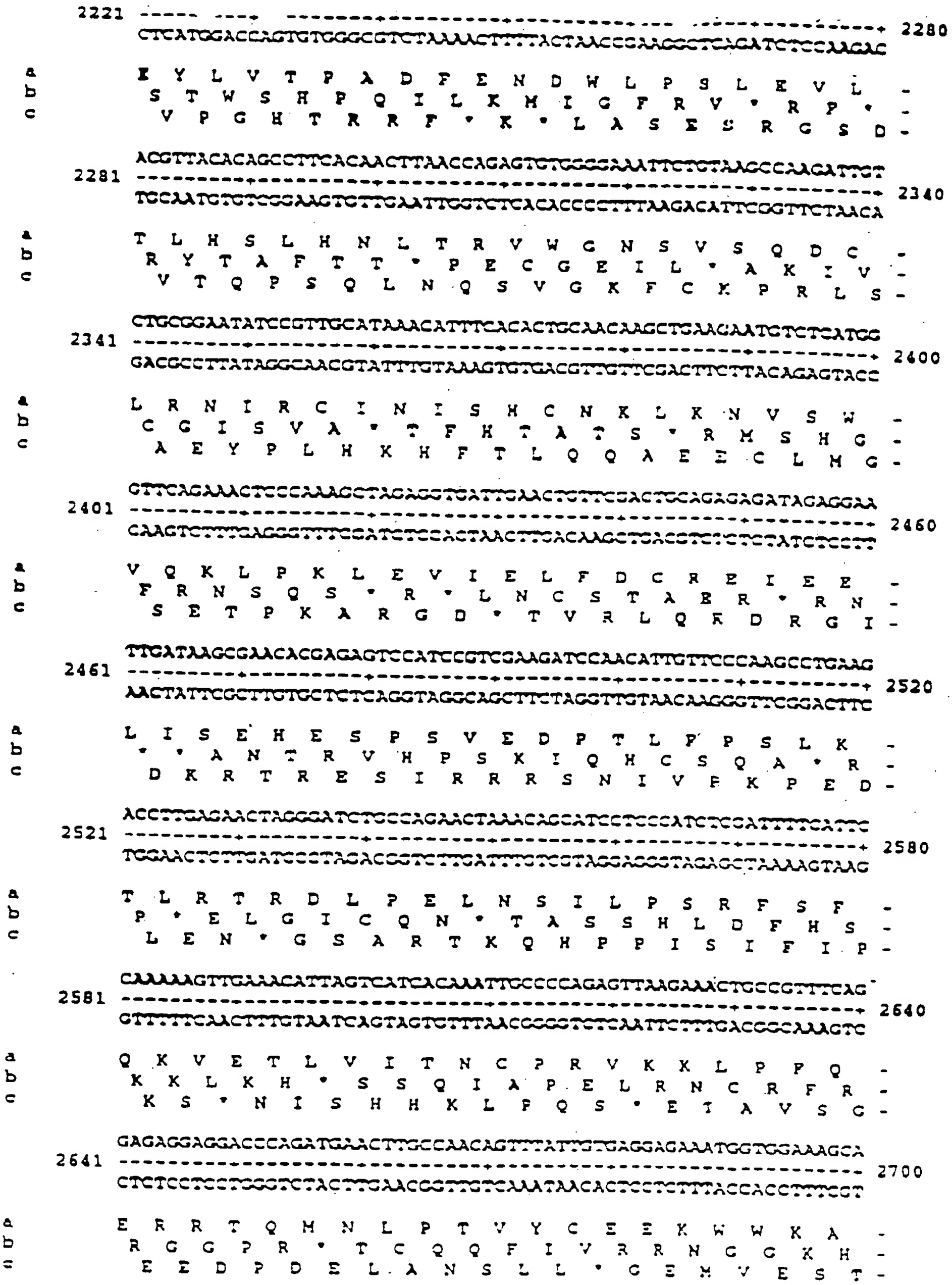


FIG. 2 CONTINUED

```
                CTGGAAAAAGATCAACCAAACGAAGAGCTTTGTTATTTACCGCGCTTTGTTCCAAATTCA
          2701  ------------+------------+------------+------------+------------+ 2760
                GACCTTTTTCTAGTTGGTTTGCTTCTCGAAACAATAAATGGCGCGAAACAAGGTTTAACT

a               L  E  K  D  Q  P  N  E  E  L  C  Y  L  P  R  F  V  P  N  *  -
b                W  K  K  I  N  Q  T  K  S  F  V  I  Y  R  A  L  F  Q  I  D  -
c                 G  K  R  S  T  K  R  R  A  L  L  F  T  A  L  C  S  K  L  I  -

                TATAAGAGCTAAGAGCACTCTGTACAAATATGTCCATTCATAAGTAGCCAGGAAGCCAGGA
          2761  ------------+------------+------------+------------+------------+ 2820
                ATATTCTCGATTCTCGTGAGACATGTTTATACAGGTAAGTATTCATCGTCCTTCGGTCCT

a               Y  K  S  *  E  H  S  V  Q  I  C  P  F  I  S  S  R  K  P  G  -
b                I  R  A  K  S  T  L  Y  R  Y  V  H  S  *  V  A  G  S  Q  E  -
c                 *  E  L  R  A  L  C  T  N  M  S  I  H  K  *  Q  E  A  R  K  -

                AGGTTGTTCCAGTGAAGTCATCAACTTTCCACATAGCCACAAAACTACAGATTATGTAAT
          2821  ------------+------------+------------+------------+------------+ 2880
                TCCAACAAGGTCACTTCAGTAGTTGAAAGGTGTATCGGTGTTTTGATCTCTAATACATTA

a               R  L  F  Q  *  S  H  Q  L  S  T  *  F  Q  N  *  R  L  C  N  -
b                G  C  S  S  E  V  I  N  F  P  H  S  H  K  T  R  D  Y  V  I  -
c                 V  V  P  V  K  S  S  T  F  H  I  A  T  K  L  E  I  M  *  S  -

                CATAAAAACCAAACTATCCGCGA
          2881  ------------+---------- 2903
                GTATTTTTGGTTTGATAGGCGCT

a               H  K  N  Q  T  I  R     -
b                I  K  T  K  L  S  A     -
c                 *  K  P  N  Y  P  R     -

Enzymes that do cut:

  NONE

Enzymes that do not cut:

    KpnI
```

FIG. 2 CONTINUED

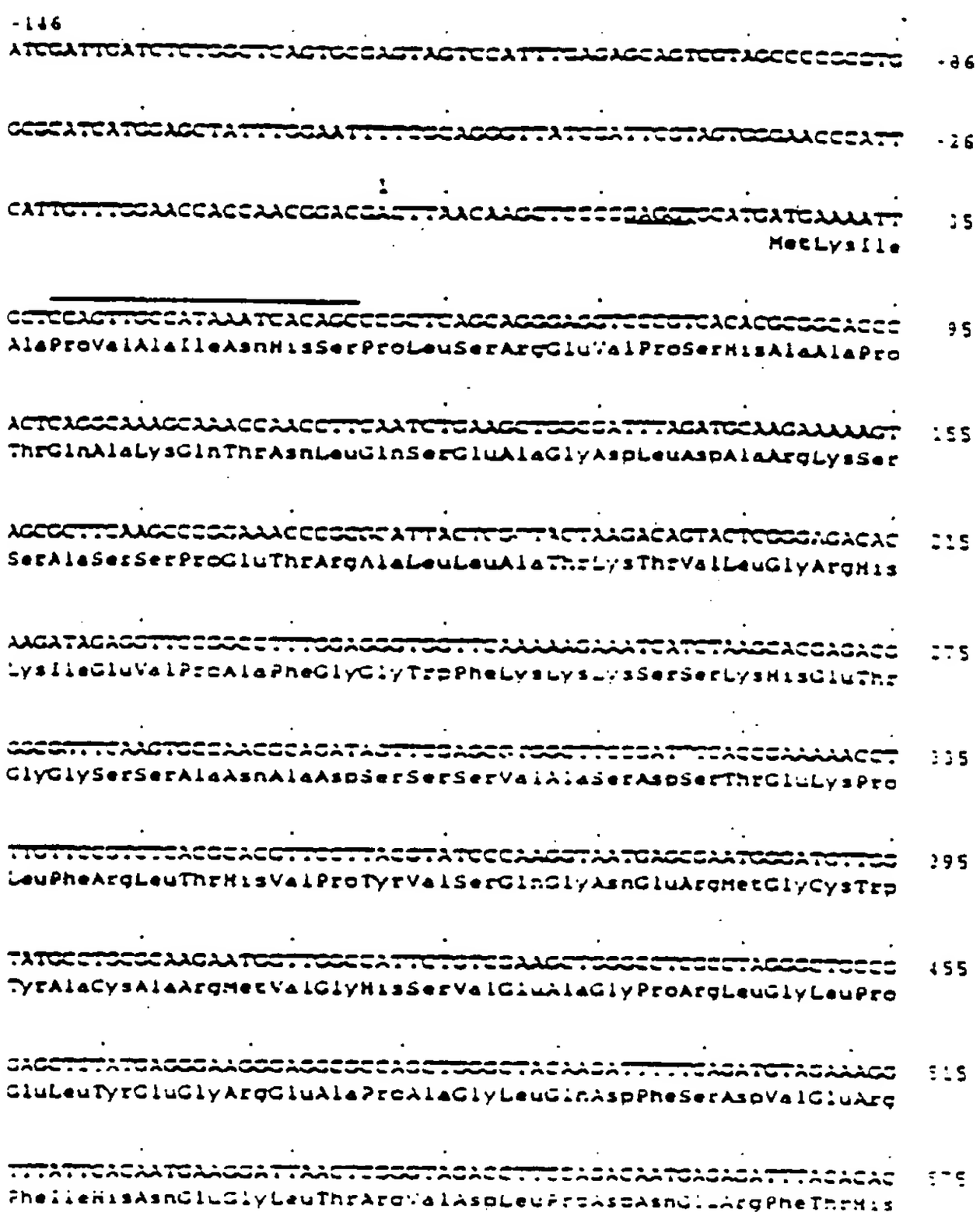

-146
-86
-26
1
35
MetLysIle
95
AlaProValAlaIleAsnHisSerProLeuSerArgGluValProSerHisAlaAlaPro
155
ThrGlnAlaLysGlnThrAsnLeuGlnSerGluAlaGlyAspLeuAspAlaArgLysSer
215
SerAlaSerSerProGluThrArgAlaLeuLeuAlaThrLysThrValLeuGlyArgHis
275
LysIleGluValProAlaPheGlyGlyTrpPheLysLysLysSerSerLysHisGluThr
335
GlyGlySerSerAlaAsnAlaAspSerSerSerValAlaSerAspSerThrGluLysPro
395
LeuPheArgLeuThrHisValProTyrValSerGlnGlyAsnGluArgMetGlyCysTrp
455
TyrAlaCysAlaArgMetValGlyHisSerValGluAlaGlyProArgLeuGlyLeuPro
515
GluLeuTyrGluGlyArgGluAlaProAlaGlyLeuGlnAspPheSerAspValGluArg
575
PheIleHisAsnGluGlyLeuThrArgValAspLeuProAspAsnGluArgPheThrHis

Figure 3.

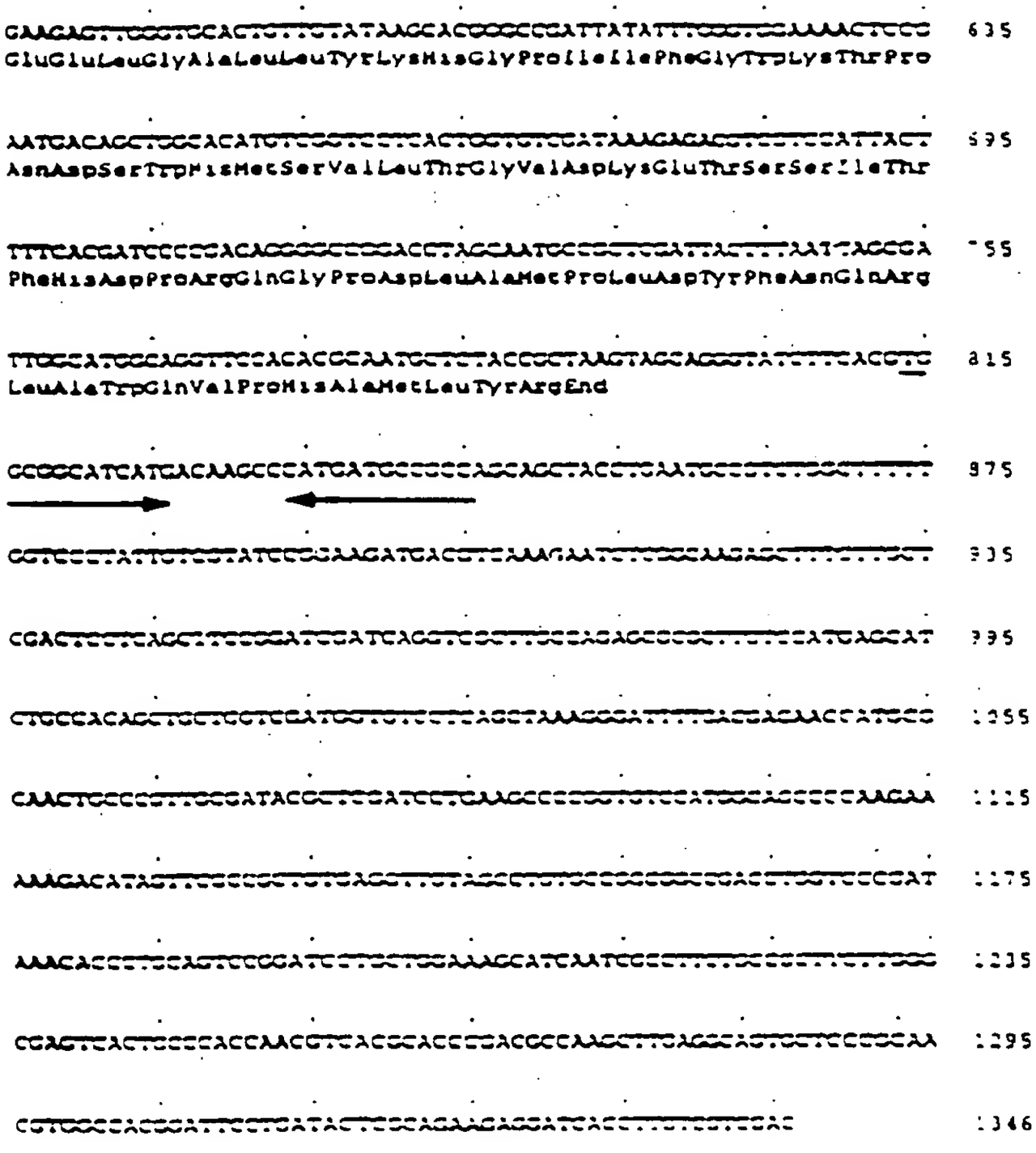


Figure 3 continued

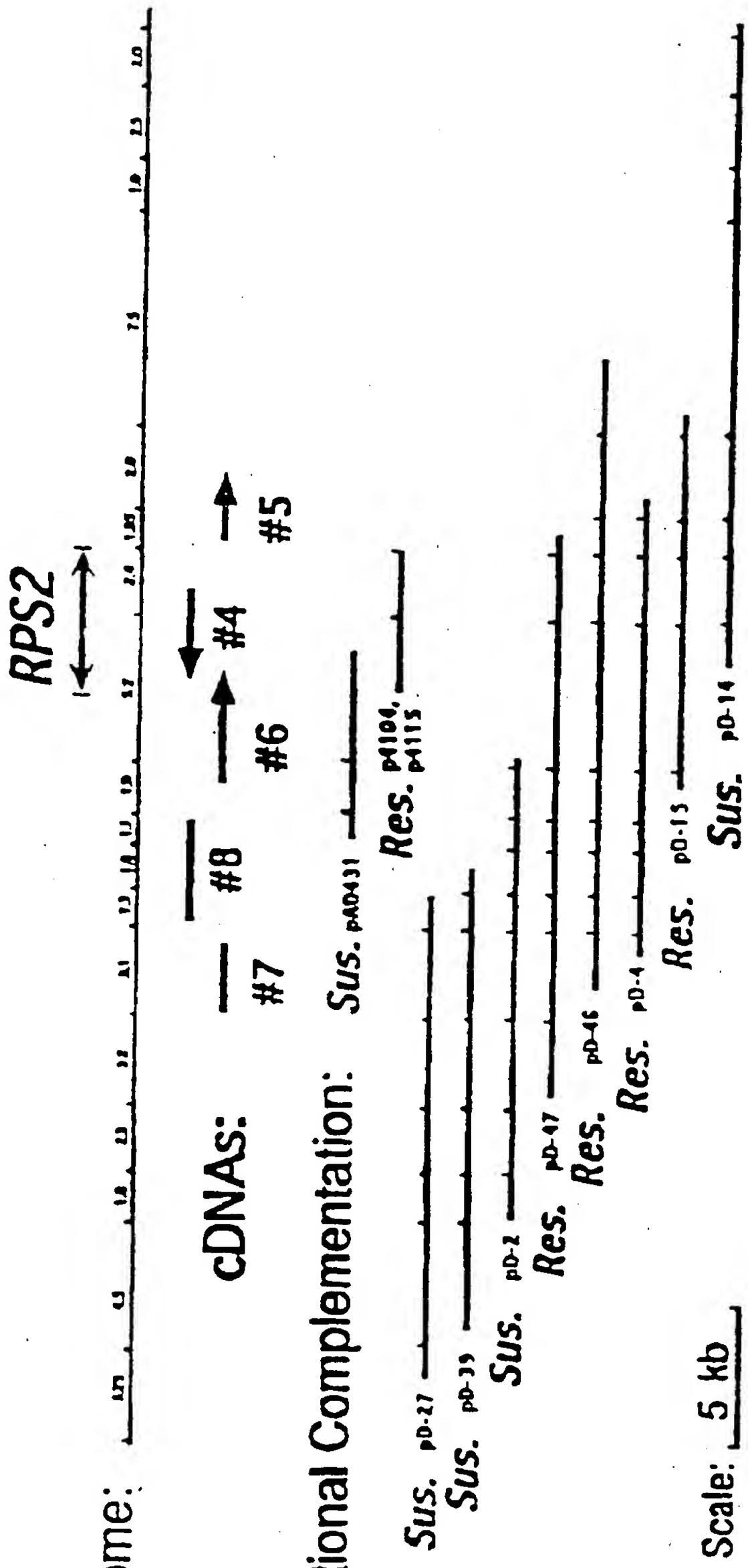

Genome:
cDNAs:
Functional Complementation:
RPS2
#8
#7
#6
#4
#5
Sus. pA0431
Res. pA1104, pA1115
Sus. pD-27
Sus. pD-33
Sus. pD-2
Res. pD-17
Res. pD-46
Res. pD-4
Res. pD-13
Sus. pD-14
Scale: 5 kb

Figure 4.

FIGURE 5A

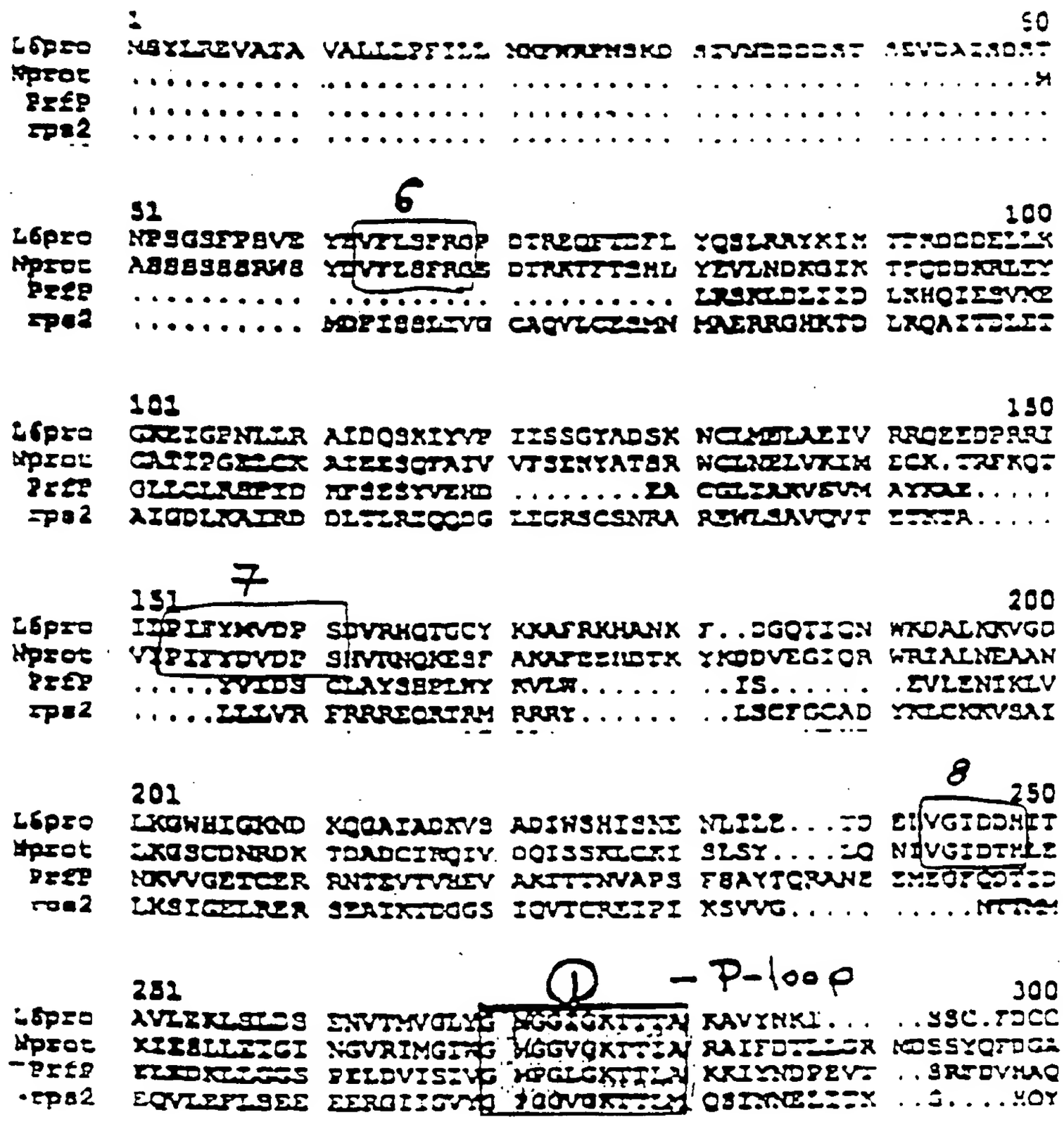


Fig. 5A (con't)

```
         301                                                    350
L6pro    CTIDNIRETQ EKDGVVVLQK KLVSEILRID ..SGSVGFNN DSGGRKTIKE
Nprot    CFLKDIKE.. NKRGMHSLQN ALLSELLR.. ...EKANYNN EEDGKHQMAS
PrfP     CVVTQLYSWR EL.LLTTIND VLEP...S.. ...DRNEKED GE.IADELRR
rps2     DVLIWVQMSR ET.GEGTIQQ AVGA...RLG ..LSWDEKET GENRALKIYR

              (2)                                 (3)
         351                                                    400
L6pro    KVARFKILVV LDDVDEKFKF EDMLGSPKDF ISQ.SRFIIT SRSMRVLGTL
Nprot    RLRSKKVLIV LDDIDNKDHY LEYLAGDLDW FGNGSRIIIT TRDKHLI...
PrfP     FLLDKRFLIL IDDVWDYKVW DNLCMCFSD. VSNRSRIILT TRLNDVAEYV
rps2     ALRGKRFLLL LDDVWEEIDL EKTGVPRPD. RENKCKVMFT TRSIALCNNM

         401                                                    450
L6pro    NEN.QCKLYE VGSMSKPRSL ELFSKHAFKK NT....PPSY YETLANDVVD
Nprot    .EK.NDIIYE VTALPDHESI QLFKQHAFGK EV....PNEN FEKLSLEVVN
PrfP     .KC.ESDPHH LRLFRDDESW TLLQKEVFQG E....SCPPE LEDVGFEISK
rps2     .GA.EYK.LR VEFLEKKHAW ELFCSKVWRK DLLESSSIRR LAEI...IVS

           (4)
         451                                                    500
L6pro    TTRGLPLTLK VIGSLLFKQE IAV..WEDTL EQL....RRT LNLDEVYDRL
Nprot    YAKGLPLALK VWGSLLHNLR LTE..WKSAI EHM....KNN .SYSGIIDNV
PrfP     SCRGLPLSVV LVAGVLKQKK KTLDSWKVVE QSLS..SQRI GSLEESISII
rps2     KCGGLPLALI TLGGAMAH.R ETEEEWIHAS EVLTRFPAEM KGMNYVFALL

          (5)           9
         501                                                    550
L6pro    KISYDALNPE .AKEIFLDIA CFFICQ..NK EEPYYMWTDC NFYPASNIIF
Nprot    KISYDGLEPK .QQEMFLDIA CFLRGE..EK DYILQILESC HIGAEYGLRI
PrfP     GFSYKNL.PH YLKPCFLYFG GFLQGKDIHD SKMTKLWVAE EFVQANN...
rps2     KFSYDNLESD LLRSCFLYCA LFPEEHSIEI EQLVEYWVGE GFLTSSHGVN

                                   10
         551                                                    600
L6pro    LIQRCMIQVG ........DD DEFKMHDQLR DMGREIVRRE DVLPHKRSRI
Nprot    LIDKSLVFIS ........EY NQVQMHDLIQ DMGKYIVNFQ KD.PGERSRL
PrfP     .......... ........EK GQEDTATRF. .EERSYW... ..........
rps2     TIYKGYFLIG DLKAACLLET GDEKTQVKMH NVVRSFALWM ASEQGTYKEL

         601                                                    650
L6pro    WSAEEGIDLL ENKKGSSKVK AISI.PWGVK YEFK.SECFL NLSELRYLHA
Nprot    WLAKEVEEVM SNNTGTMAME AIWVSSYSST LRFS.NQAVK NMKRLRVFNM
PrfP     .......... .......... .......... .......... ..........
rps2     ILVEPSMGHT EAPKAENWRQ ALVISLLDNR IQTL.PEKLI CPKLTTLMLQ

         651                                                    700
L6pro    REAMLTGDFN NLLPNLKWLE LPFYKHGEDD PPLTNYTMKN LII.VILEHS
Nprot    GRSSTHYAID YLPNNLRCFV CTNYPW...E SFPSTFELKM LVH.LQLRH.
PrfP     .......... .......... .......... .......... ..........
rps2     QNSSLKKIPT GFFMHMPVLR VLDLSF.... TSITEIPLSI KYL.VELYHL

         701                                                    750
```

Fig 5A(con't)

```
L6pro   HITADDHCCN RDDGGMAERL KVVRLASNYS LYGRRVR... ..........
Nprot   .......NSL RKLWTITKHL PSL....... ...RRID... ..........
PrfP    .......... .......... .......... .......... ..........
rps2    SMSGTKISVL SQELGNLRKL KHLDLQRTQF LQTIPRDAIC WLSKLEVLNL

        781                                               800
L6pro   .LSD.CMRFP KSIEVLSMTA IEMDEVDIGE LKKLKTLVLK FCPIQKISGG
Nprot   .LSW.SKRLT RTPDFTGMPN LEY..VNLYQ CSNLEEVHHS LGCCSKVIGL
PrfP    .......... .......... .......... .......... ..........
rps2    YYSY.AGWEL QSFGEDEAEE LGFADLEYLE NLTTLGITVL SLETLKTLFE

        801                                               850
L6pro   TFGMLKGLRE L.CLEFSWGT NLRSVVADIG CLSSLKVLKT TGAKEVEINE
Nprot   YLNDCKSLKR F.......... .......... .......... .PCVNVESLE
PrfP    .......... .......... .......... .......... ..........
rps2    FGALHKHIQH L.HVEECNEL LYFNLPSLTN HGRNLRRLSI KSCHDLEYLV

        851                                               900
L6pro   FFLGLK.... ...ELSTSSR IFNLSQLLDL EVLKVYDCKD CFDMPPASPS
Nprot   Y.LGLR.... ...SCDSLEK LPEIYGRMKP EI........ QIHMQGSGIR
PrfP    .......... .......... .......... .......... ..........
rps2    TPADFENDWL PSLEVLTLHS LHNLTRVWGN SVSQDCLRNI RCINISHCNK

        901                                               950
L6pro   EDESSVWWKV SKLKSLQLEK TRINVNVVDD ASSGGHLPRY LLPTSLTYLK
Nprot   ELPSSIFQYK THVTKLLL.. .MGGGNLVAL PSSICRL... ...KSLVSLS
PrfP    .......... .......... .......... .......... ..........
rps2    LKNVSWVQKL PKLEVIELFD CREIEELISE HESPSVEDPT LFP.SLKTLR

        951                                              1000
L6pro   IYQCTEPTWL P.GIENLENL TSLEVNDIFQ TLGGDLDGLQ GLRSLEILRI
Nprot   VSGCSKLESL PEEIGDLDNL RVFDASDTL. .......... ......ILRP
PrfP    .......... .......... .......... .......... ..........
rps2    TRDLPELNSI LPSRFSFQKV ETLVITNCPR VKKLPFQERR TQMNLPTVYC

        1001                                             1050
L6pro   RKVNGLARIK GLKDLLCSST CKLRKFYITE CPDLIELLPC ELGVQTVVVP
Nprot   P......... .......SSI IRLNKLIILM FRGFKDGVHF EFPPVAEGLH
PrfP    .......... .......... .......... .......... ..........
rps2    EEKWWKALEK DQPNEELCYL PRFVPN.... .......... ..........

        1051                                             1100
L6pro   SMAELTIRDC PRLEVGPMIR SLPKFPMLKK LDLAVANITK EEDLDAIGSL
Nprot   SLEYLNL.SY CNLIDGGLPE EIGSLSSLKK LDLSRNNF.. EHLPSSIAQL
PrfP    .......... .......... .......... .......... ..........
rps2    .......... .......... .......... .......... ..........

        1101                                             1150
L6pro   EELVSLELEL DDTSSGIERI VSSSKLQKLT TLVVKVPSLR EIEGLEELKS
```

Fig. 5A(con't)

```
Mprot  GALQSLDLK. .......... .DCQRLTCLP ELPPELNILH .VDCMMALRT
PrtP   .......... .......... .......... .......... ..........
rps2   .......... .......... .......... .......... ..........

                                                          1200
       1151
L6pro  LQDLYLEGCT SLQRLPLEKL KE.....LD IQGCPDLTEL VQTVVAVPCL
Mprot  IHDL.VTKRK KLHRVKLDCA HNDTMYNLFA YTTPQNISSM RHDISASDSL
PrtP   .......... .......... .......... .......... ..........
rps2   .......... .......... .......... .......... ..........

       1201                                               1250
L6pro  RQLTTRDCPR LEVQPMIQSL PKFPMLNELT LSMVNITKCD SLEVLGSLEE
Mprot  .SLTV..... FTGQPYPSTC PSWPHHQGWD .SSVSVNLPS NMYIPDKGLC
PrtP   .......... .......... .......... .......... ..........
rps2   .......... .......... .......... .......... ..........

       1251                                               1300
L6pro  LD.SLELTLD DTGSSIERLS FLSKLGKLTT LIVEVPSLKS IESLAELNSL
Mprot  FAVCYSRSLI DTTAHLIPVC .DDRMSRMTQ KLALSECGTS ESNYSEWD.I
PrtP   .......... .......... .......... .......... ..........
rps2   .......... .......... .......... .......... ..........

       1301                                               1350
L6pro  RILYL..... .......... .EGCTSLERL WPDQGQLGSL KNLAVLDIQG
Mprot  HPFFVPFAQL WDTSKANGKT PNDYGIIRLS FSGLEKMTGL RLLYKEGPEV
PrtP   .......... .......... .......... .......... ..........
rps2   .......... .......... .......... .......... ..........

       1351                                    1387
L6pro  CKSLSVDHLS ALKTILPPFA RITHPDQPYR .......
Mprot  NALLQMGENS NEPTEHSTGI RRTQYNNRTS FYELINC
PrtP   .......... .......... .......... .......
rps2   .......... .......... .......... .......
```

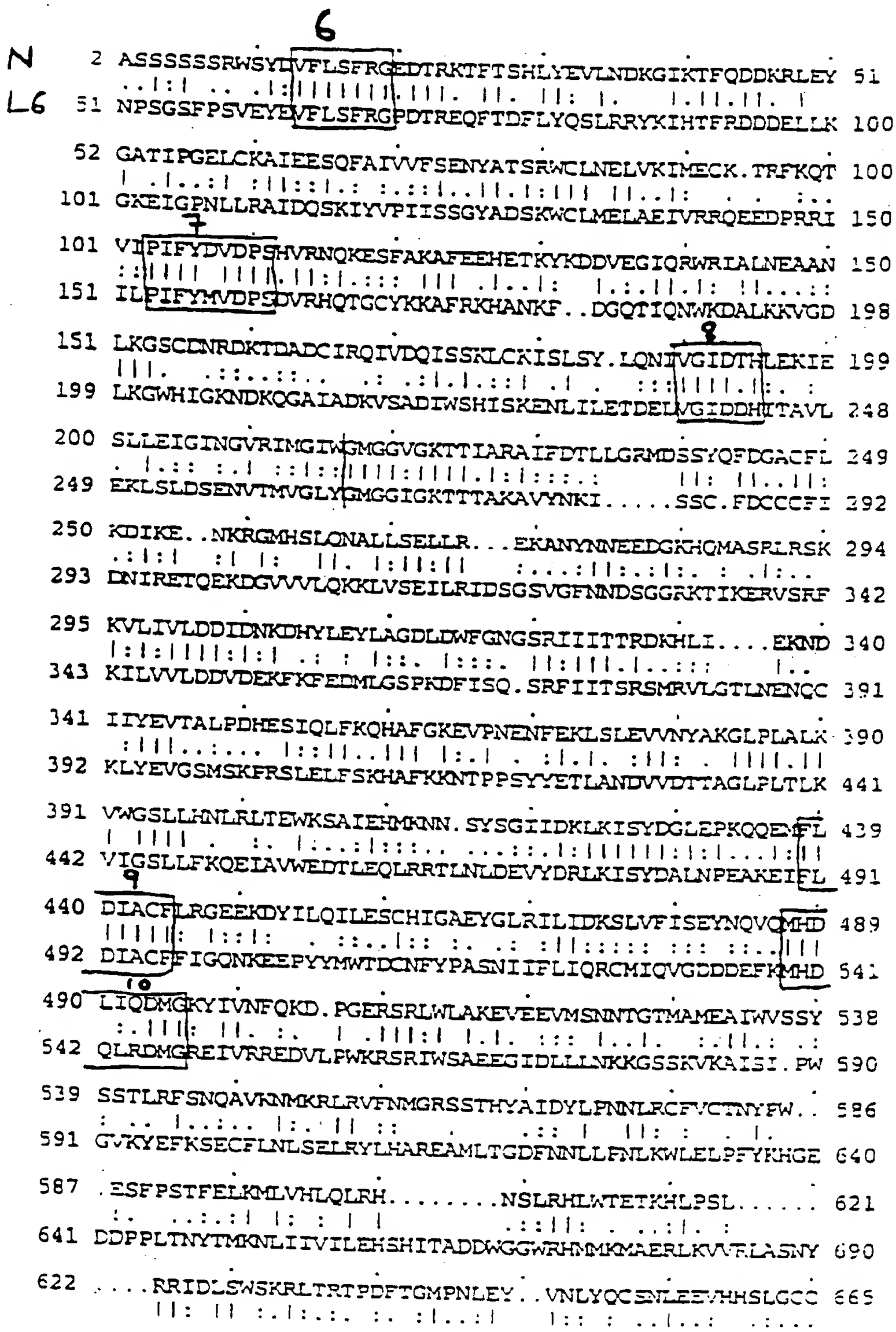


FIGURE 5B

```
691 SLYGRRVRLSDCWRFPKSIEVLSMTAIEMDEVDIGELKKLKTLVLKFCPI 740
666 SKVIGLYLNDCKSLKRFPCVNVESLEYLGLRSCDSLEKLPEIYGRMKP.. 713
741 QKISGGTFGMLKGLREL.........CLEFNWGTNLREVVADIGQLSSLK 781
714 ........EIQIHMQGSGIRELP.SSIFQYKTHVTKLLLWNM....KNLV 750
782 VLKTTGAKEVEINEFPLGLKELSTSSRIPNLSQLLDLEVLKVYDCKDGFD 831
751 ALPSSICRLKSLVSLSVSGCSKLESLPEEIGDLDNLRVFDASDTLILRP. 799
832 MPPASPSEDESSVWWKV...SKLKSLQLEKTRINVNVVDDASSGGHLPRY 878
800 ....................PSSIIRLNKLIILMFRGFKDGVHFEFPPVAE 830
879 LLPTSLTYLKIYQCTEPTWLPGIENLENLTSLEVNDIFQTLGGDLDGL.Q 927
831 GLHSLEYLNLSYCNLID..GGLPEEI.GSLSSLKKLDL..SRNNFEHLPS 875
928 GLRSLEILRIRKVNGLARIKGLKDLLCSSTCKLRKFYITECPDLIELLPC 977
876 SLA....QLGALQSLDLKDCQRLTQLPELPPELNELHVDCHMALKFIHYL 921
978 ELGVQTVVVPSMAELTIRDCPRL.EVGPMIRSLPKFPM.....LKKLDLA 1021
922 VTKRKGLHRVKLDDAHNDTMYNLFAYTMFQNISSMRHDISASDSLSLTVF 971
1022 VANITKEEDLDAIGSLEELV..SLELELDDTSSGIERIVSSSKLQKLTTL 1069
972 TGQPYPEKIPSWFHHQGWDSSVSVN.......LPENWYIPDKFLGFAVCY 1014
1070 VV.....KVPSLREIEGLEELKSLQDLYLEGCTSLGRLPLEKLKELDIGG 1114
1015 SRSLIDTTAHLIPVCDDK..........MSRMTQKLA....LSECDTES 1049
1115 CPDLTELVQTVVAVPSLRGLTIRDCPRLEVGPMIQSLPKFPMLNELTLSM 1164
1050 SNYSEWDIHFFFVPFAGLWDTSKANGKTPNDYGIIRLSFSGEEKMYGLRL 1099
1165 VNITKEDELEVLGSLEELDSLELTLDDTCSSIERISF.LSKLQKLTTLIV 1213
1100 LYKEGPEVNALLQMRENSNEPTEHSTGIRRTQYNNRTSFYELIN 1143
1214 EVPSLREIEGLAELKSLRILYLEGCTSLER.LWPDQQQLGSLKN 1256
```

FIGURE 5B (CON'T)

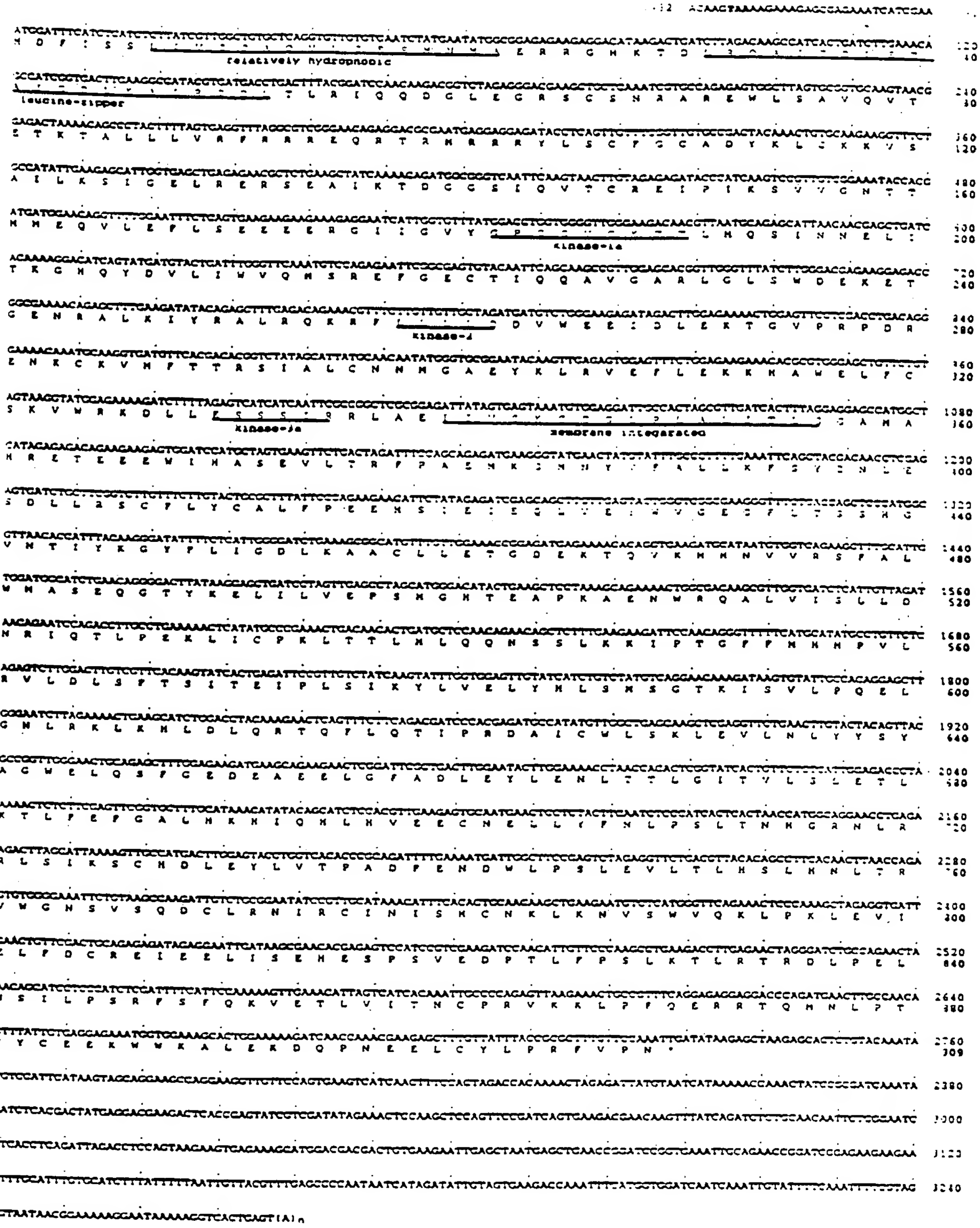

relatively hydrophobic
leucine-zipper
kinase-1a
kinase-1
kinase-2a
membrane integrated

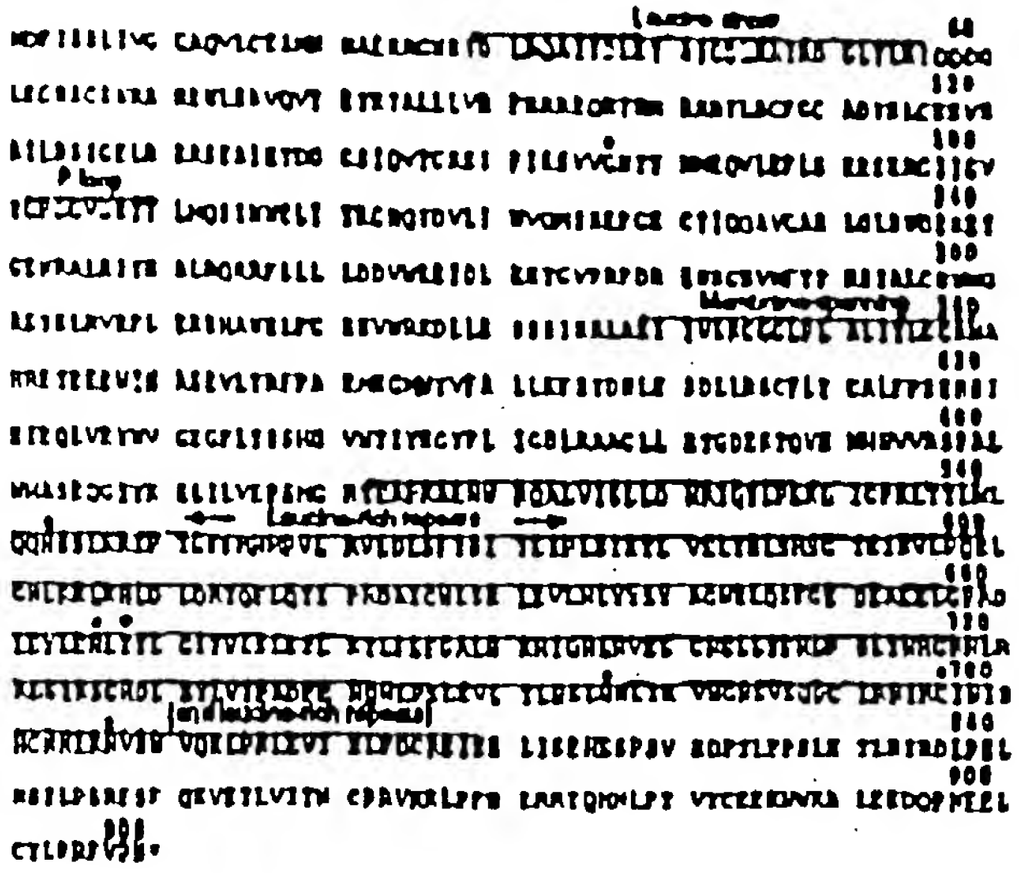
FIGURE 6

```
consensus    PXXaXX LXXLXXLXaXXXX aXXa

505    PKAENW RQALVISLLD NR IQTL
527    PEKLIC PK LTTLMLQQNSSLKKI
550    PTGFFMHMPVLRVLDLSFTS ITEI
574    PLSIKY LVELYHLSMSGTK ISVL
597    PQELGN LRKLKHLDLQRTQFLQTI
621    PRDAICWLSKLEVLNLYYSYAGWEL  QSFGEDEAEELG
658    FADLEY LENLTTLGITVLS LETL  KT
683    LFEFGALHKHIQHLHVEECNELLYF  NL
710    P SLTNHGRNLRRLSIKSCHDLEYL  YT
736   PADFENDWLPSLEVLTLHSLHNLTRV  NGN
765    SVSQDC LRNIRCINISHCNKLKNV  SWVQKL
795    PK LEV IELFDCREIEELISEHES  PSVED
823    PT LFPSLKTLRTRDLPELNSI  L
845    PSRFS  FQKVETLVITNCPRVKKL
```

FIGURE 7

FIGURE 8



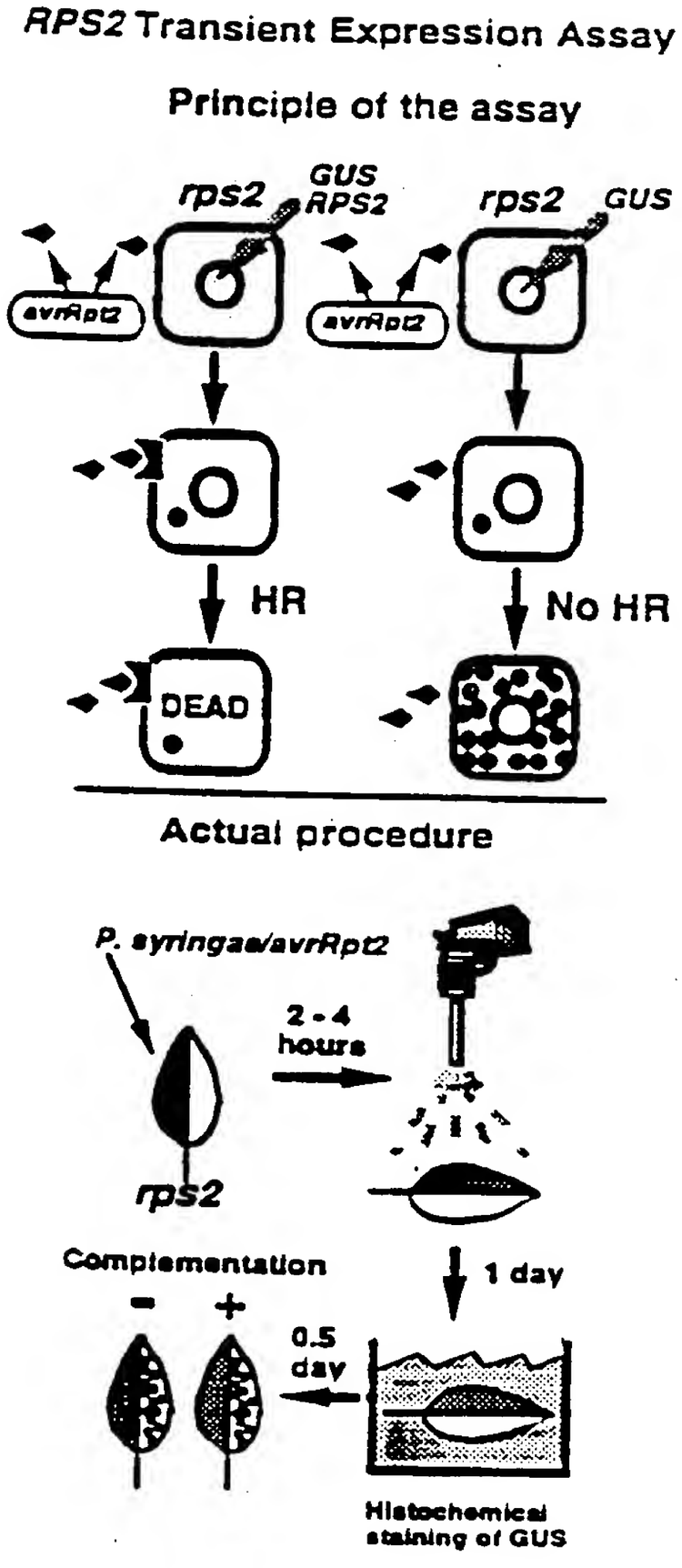

RPS2 Transient Expression Assay
Principle of the assay
rps2
GUS RPS2
avrRpt2
rps2
GUS
avrRpt2
HR
No HR
DEAD
Actual procedure
P. syringae/avrRpt2
2 - 4 hours
rps2
Complementation
1 day
0.5 day
Histochemical staining of GUS

FIGURE 9

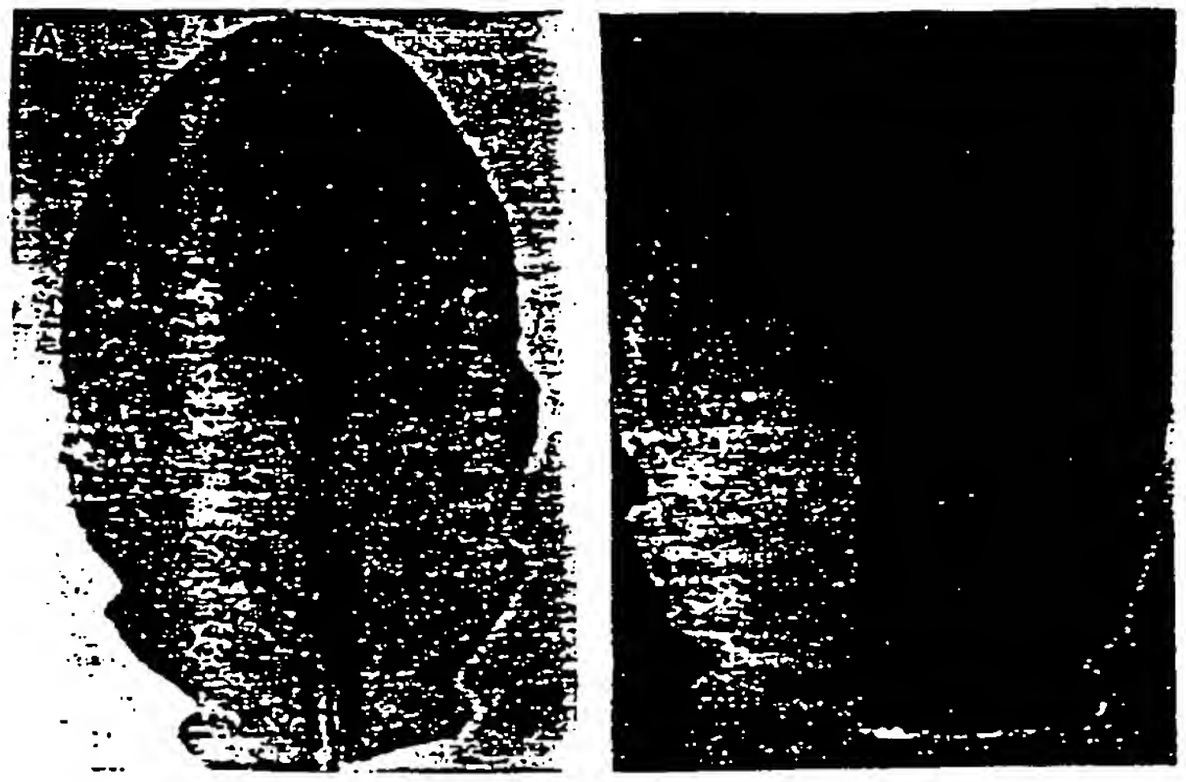


FIGURE 10

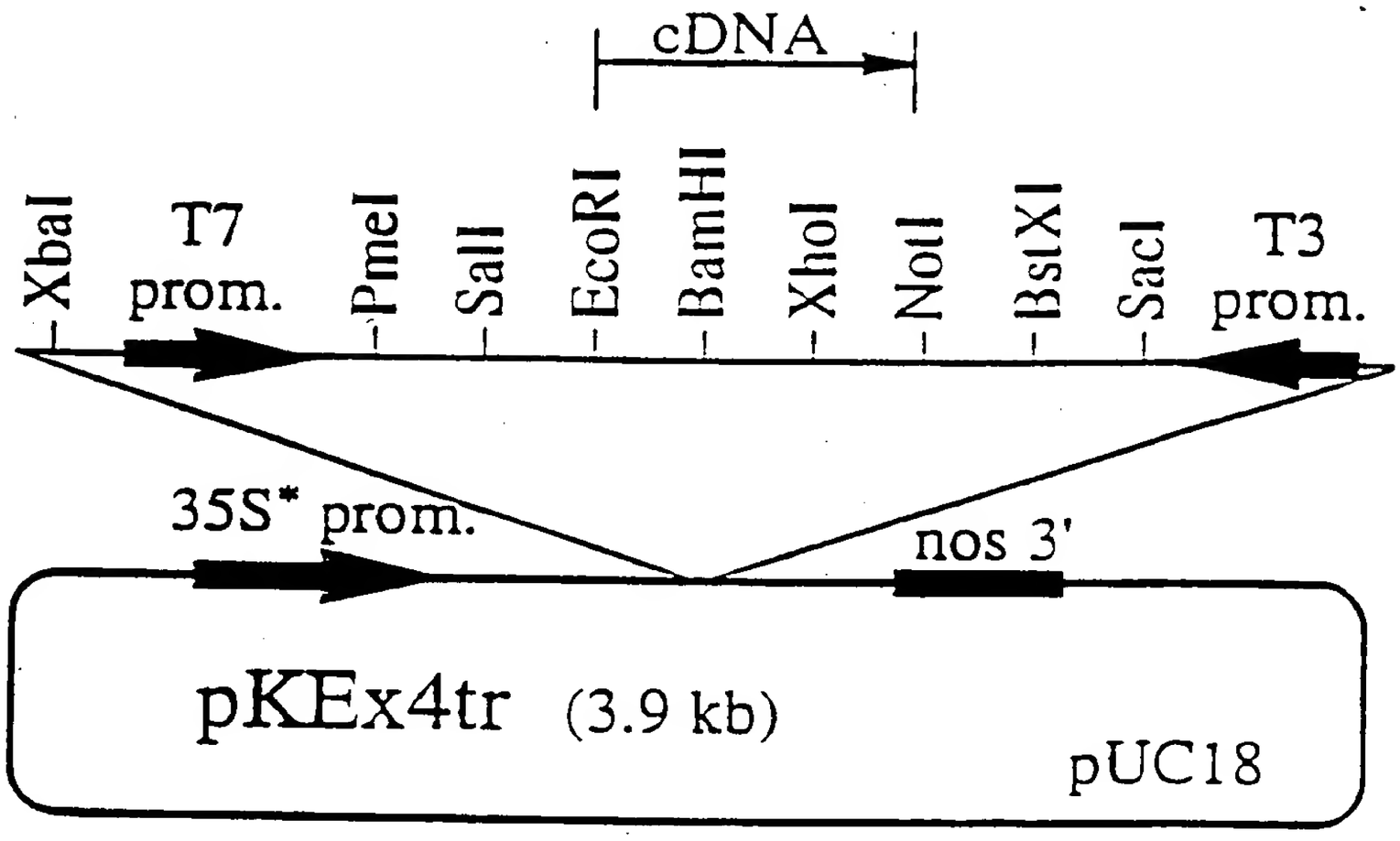

cDNA
XbaI
T7 prom.
PmeI
SalI
EcoRI
BamHI
XhoI
NotI
BstXI
SacI
T3 prom.
35S* prom.
nos 3'
pKEx4tr (3.9 kb)
pUC18

FIGURE 11

```
      1   10        1   20        30        1   40        50        60
   1 aagctttaca gattggatga tctcttaatg catgctgaag tgactgcaaa aagggtagca 60
  61 atattcagtg gttctcgtta tgaatatttc atgaacggaa gcagcactga gaaaatgagg 120
 121 ccctttgttat ctgatttttct gcaagagatt gagtctgtca aggtagagtt cagaaatgtt 180
 181 tgcttgcaag ttctggatat atcacctttt tccctgacag atggagaagg ccttgttaat 240
 241 ttcttattaa aaaaccaggc caaggtgccg aatgatgatg ctgtttcttc tgatggaagt 300
 301 ttagaggatg caagcagcac tgagaaaatg ggacttccat ctgatttttct ccgagagatt 360
 361 gagtctgttg agataaagga ggccagaaaa ttatatgatc aagttttgga tgcaacacat 420
 421 tgtgagacga gtaagacaga tggaaaaagc tttatcaaca ttatgttaac ccaacaggac 480
 481 aaggtgctgg actatgatgc tggttcagtc tcttatcttc ttaaccaaat ctcagtagtt 540
 541 aaagacaaac tattgcacat tggctcttta cttgtagata ttgtacagta ccggaatatg 600
 601 catatagaac ttacagatct cgctgaacgt gttcaagata aaaactacat tcgtttcttc 660
 661 tctgtcaagg gttatattcc tgcttggtat tacacactat atctctctga tgtcaagcaa 720
 721 ttgcttaagt ttgttgaggc agaggtaaag attatttgtc tgaaagtacc agattcttca 780
 781 agttatagct tccctaagac aaatggatta ggatatctca attgcttttt aggcaaatTC 840
 841 gaggagcttt tacgttctaa gctcgatttg ataatcgact taaaacatca gattgaatca 900
 901 gtcaaggagg gcttattgtg cctaagatca ttcattgatc attttcaga aagctatgtt 960
 961 gagcatgatg aagcttgtgg tcttatagca agagtttctg taatggcata caaggctgag 1020
1021 tatgtcattg actcatgctt ggcctattct catccacttt ggtacaaagt tctttggatt 1080
1081 tctgaagttc ttgagaatat taagcttgta aataaagttg ttggggagac atgtgaaaga 1140
1141 aggaacactg aagttactgt gcatgaagtt gcaaagacta ccactaatgt agcaccatct 1200
1201 ttttcagctt atactcaaag agcaaacgaa gaaatggagg gttttcagga tacaatagat 1260
1261 gaattaaagg ataaactact tggaggatca cctgagcttg atgtcatctc aatcGttggc 1320
1321 atgccaggat tgggcaagac tacactagca aagaagattt acaatgatcc agaagtcacc 1380
1381 tttcgctttg atgtccatgc tcaatgtgtt gtgactcaat tatattcatg gagagagttg 1440
1441 ttgctcacca ttttgaatga tgtgcttgag ccttctgatc gcaatgjaaa agaagatgga 1500
1501 gaaatagctg atgagctacg ccgatttttg ttgaccaaga gattccttgat tctcattgat 1560
1561 gatgtgtggg actataaagt gtgggacaat ctatgtatgt gcttcagtga tgttcaaat 1620
1621 aggagtagaa ttatcctaac aacccgcttg aatgatgtcg ccgaatatgt caaatgtgaa 1680
1681 agtgatcccc atcatcttcg tttattcaga gatgacgaga gttggacatt attacagaaa 1740
1741 gaagtctttc aaggagagag ctgtccacct gaacttgaag atgtgggatt tgaaatatca 1800
1801 aaaagttgta gagggttgcc tctctcagtt gtgttagtag ctggtgttct gaaacagaaa 1860
1921 agcttggaag agagcatatc tataattgga ttcagttacA agaatttacc acactatctt 1980
1981 aagccttgtt ttctctattt tGgaggattt ttgcagggaa aggatattca tgActcaaaa 2040
2041 atgaccaagt tgtgggtagc tgaagAgttt gtacaagcaa acaacgaaaa aggacaagaa 2100
2101 gataccccca caaggtttct tggacgatct tattggtagg aatctggtga tggccatgga 2160
2161 gaagagacct aaTgccaagg tgaaaacgtg ccgcattcat gatttgttgc ataaattctg 2220
2221 catggaaaag gccaaacaag aggatttcct tctccagatc aataggtaaa aaaaactgta 2280
2281 ttaattttac attacaaaaa aaaagaactg tattaatttt actgtattat gtttatgcca 2340
2341 actctcattt ccatgtgttc tcttttattc aatcagtgg agaaggtgta tttcctgaac 2400
2401 gattggaaga ataccgattg ttcgttcatt cttaccaaga tgaaattgat ctgtggcgcc 2460
2461 catctcgctc taatgtccgc tctttactat tcaatgcaat tgatccagat aacttgttat 2520
2521 ggccgcgtga tatctcctte atttttgaga gcttcaagct tgttaaagtg ttggatttgg 2580
2581 aatcattcaa cattggtggt actttttcca ttgaaataca atatctaatt cagatgaagt 2640
2641 actttgcggc tcaaactgat gcaaattcaa ttcattcatc tatagctaag cttgaaaatc 2700
2701 ttgagacttt tgtcgtaaga ggattgggag gagagatgat attaccttgt tcacttctga 2760
2761 agatggtgaa attgaggcat atacatgtaa atgatcgggt ttcttttggt ttgcgtgaga 2820
2821 acatggatgt tttaactggt aactcacaat tacctaattt ggaaaccttt tctactccgc 2880
2881 gtctcttttta tggtaaagac gcagagaaga ttttgagggaa gatgccaaaa ttgagaaaat 2940
2941 tgagttgcat attttcaggg acatttggtt attcaaggaa attgaagggt aggtgtgttc 3000
3001 gttttcccag attagatttt ctaagtcacc ttgagtcccct caagctggtt tcgaacagct 3060
3061 atccagccaa acttcctcac aagttcaatt tcccctcgca actaagggaa ctgacttttat 3120
3121 caaagttccg tctaccttgg acccaaattt cgatcattgc agaactgccc aacttggtga 3180
3181 ttcttaagtt attgctcaga gcctttgaag gggatcactg ggaagtgaaa gattcagagt 3240
3241 tcctagaact caaatactta aaactggaca acctcaaagt tgtacaatgg tccatcttctg 3300
3301 atgatgcttt tcctaagctt gaacatttgg ttttaacgaa atgtaagcat cttgagaaaa 3360
3361 tccccttctcg ttttgaagat gctgtttgtc taaatagagt tgaggtgaac tggtgcaact 3420
3421 ggaatgttgc caattcagcc caagatattc aaactatgca acatgaagtt atagcaaatg 3480
3481 attcattcac agttactata cagccttcag attggtctaa agaacagccc cttgactctt 3540
3541 agcaaaggtt tgttcttgct gtgttcatcc aagtgcattt aacatttatt catttgttt 3600
3601 tacaccagaa catgtttatt ttgctagtat tacttgatac attaaaagaa atcgaactca 3660
3661 tatttctgct acagtcttaa cttttccttgg gcttacttga ggtctagatt agatcaatgg 3720
3721 ttcatgtaat ttttaattca ctgtttcatt caactgtctt atgtagttg tgaaatgaca 3780
3781 atattgttat ccctagccaa atttattatg ttcaaatgaa aactgatgtc acaactactt 3840
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FIGURE 12

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3841 ttttgtgaaa tgttttt    tt-. .gcta taaaattgac gaattgacag ctt    ..  )00
3901 tgtcagctaa actctttg.c accagaagtg tatttagaat tactgtggtt ttatgaaaga 3960
3961 gttctgtaga attttatgct tttgcagaat atagtttaaa acaacaacac ttctctgttt 4020
4021 cagagatagc agaagctaaa gttcaaggca ttttgtttat ttctagaaca agtggagttc 4080
4081 ttatgttgaa ttcttgaaaa gaagaagaat caggagcagg taaagttatc tctttttatg 4140
4141 ttttttcttct tttagatgtt atttcttcat cttgaacgtg aacaccgctg aaagcatttt 4200
4201 aataaaaccg gagagaaaaa taagatcttt ttatataaag cattatcatg taaatatgcc 4260
4261 taaatccata tggtacaact gtttgacaaa atgatagaga ggggagtttt atagtataag 4320
4321 taaaacagga ttgagaaaaa aatccttgca cgattttcaa tttctggcca catcacaatg 4380
4381 tgtgtcaaag ttcccctctt taagtggaac aagcaatcag aaaagcTcat tcttatcggt 4440
4441 gacataccaa taccagctga ctgtctcatc ttggttaact tagccttgct tacttagact 4500
4501 attagattag ttactaatga actggtaaat tggaaccaaa tgtagttagc ttgatgagct 4560
4561 ggtagacatg tatatatgaa gatacacgcg taactttagt cgatggttaa tttttcattt 4620
4621 tcgatttttt ttctttcacag agtatatatg actttggccta aaagtttttg cttcactaat 4680
4681 ttaactatta ccgtggatga aacaagcatg gcaacatttt caacaactat cactcaagca 4740
4741 atgtaaaaaa tggaggttct acgagcggta catgtaagag ttttgtgcac acaagaggtt 4800
4801 ctgagacttg aaccatccat gtccaaggca gttgagatgc tagtaaagaa agaagaagat 4860
4861 gagcctgcac taattaatct ccctgtatga atgagagaat gagaaaaaga tggagcttca 4920
4921 tgaaccaaaa gttacctttt tttttcttc ttaatggcat tactttgaag cacatgtttg 4980
4981 ttagttgtaa attgtaatgg tgaagtgttt gtaaatatag ggagtgatat ttgaaagaat 5040
5041 ggttgtgtta tctttacaaa ccggaatcat ttctgtataa ttttcttctg taatttttgg 5100
5101 tttcggttta ttcattactc atttcagtaa gctt                            5134
          | 10       | 20       | 30       | 40       | 50       | 60
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FIGURE 12 (CON'T)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/04589

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07K 14/415; C12N 15/29; C12Q 1/68
US CL : 536/23.1, 23.6, 24.3; 435/6; 530/370

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 23.6, 24.3; 435/6; 530/370

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MPSRCH, SDC, CAS ONLINE, IG
Search terms: SEQ ID NOS: 1-5, 105, 158, AND 191

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X ----- P, Y	Cell, Volume 78, issued 23 September 1994, S. Whitham et al., "The product of the tobacco mosaic virus resistance gene *N*: Similarity to Toll and the interleukin-1 receptor", pages 1101-1115, see sequences.	1, 10-13 ------- 14, 19-32
P, X ----- P, Y	Science, Volume 265, issued 23 September 1994, A.F. Bent et al., "*RPS2* of *Arabidopsis thaliana*: a leucine-rich repeat class of plant disease resistance genes", pages 1856-1860, see the entire document.	10-14, 19-32 ------- 1
P, X ----- P, Y	Cell, Volume 78, issued 23 September 1994, M. Mindrinos et al., "The A. thaliana disease resistance gene *RPS2* encodes a protein containing a nucleotide-binding site and leucine-rich repeats", pages 1089-1099, see the entire document.	10-14, 19-32 ------- 1

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
13 JULY 1995

Date of mailing of the international search report
04 AUG 1995

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/04589

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Proceedings National Academy of Sciences, USA, Volume 90, issued December 1993, F. Bunz et al., "cDNAs encoding the large subunit of human replication factor C", pages 11014-11018, see peptide sequences.	14
X	Proceedings National Academy of Sciences, USA, Volume 90, issued December 1993, P.D. Burbelo, et al., "Cloning of the large subunit of activator 1 (replication factor C) reveals homology with bacterial DNA ligases", pages 11543-11547, see peptide sequences.	14
X	Biochem. Biophys. Res. Commun., Volume 193, Number 2, issued 15 June 1993, Y. Lu, et al., "Cloning and expression of a novel human DNA binding protein, PO-GA", pages 779-786, see peptide sequences.	14
Y	The Plant Cell, Volume 5, issued August 1993, B.N. Kunkel et al, "*RPS2*, an Arabidopsis disease resistance locus specifying recognition of *Pseudomonas syringae* strains expressing the avirulence gene *avrRpt2*", pages 865-875, see the entire document.	1, 10-14, and 19-32
Y	Phil. Trans. R. Soc. Lond. B, Volume 342, issued 29 November 1993, C. Dean, "Advantages of Arabidopsis for cloning plant genes", pages 189-195, see especially Table 1.	1, 10-14, 19-32

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/04589

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 10-14, 19-32

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/04589

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-32, drawn to RPS oligos and polypeptides.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

1. The oligos of claim 1
2. The oligos of claim 2.
3. The oligos of claim 3.
4. The oligos of claim 4.
5. The oligos of claim 5.
6. The oligos of claim 6.
7. The oligos of claim 7.
8. The oligos of claim 8.
9. The oligos of claim 9.

and

1. The peptides of claim 14.
2. The peptides of claim 15.
3. The peptides of claim 16.
4. The peptides of claim 17.
5. The peptides of claim 18.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each group of oligos comprise a separate and distinct chemical entity which does not share a special technical feature with any other species. Likewise, each group of peptides comprise a separate and distinct chemical entity which does not share a special technical feature with any other species of peptide.

Group II, claims 33-37, drawn to identification of plant disease resistance using biolistics.

Group III, claim 38, drawn to an antibody.

Group IV, claim 39-40, drawn to the Prf amino acid sequence.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I is drawn to specific products and the use of those products to isolate disease resistance genes while Group II is not drawn to the use of any specific product to isolate genes but rather to the use of biolistics to isolate genes. The use of biolistics is a different inventive concept than the use of the specific products of Group I. Therefore, Groups I and II do not share a special technical feature.

The inventions listed as Groups I and III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group III is drawn to an antibody which is a product that is chemically distinct from the products of Group I which are specific oligos and peptides. Therefore, Groups I and III do not share a special technical feature.

The inventions listed as Groups I and IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I is drawn to specific nucleotides and peptides related to RPS while Group IV relates to a Prf amino acid sequence. These appear to be separate and distinct chemical entities. Therefore, Groups I and IV do not share a special technical feature.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/04589

The inventions listed as Groups II and III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the antibodies of Group III could not be used in the method of Group II. Therefore, Groups II and III do not share a special technical feature.

The inventions listed as Groups II and IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the Prf amino acid sequence of Group IV could not be used in the method of Group II. Therefore, Groups II and IV do not share a special technical feature.

The inventions listed as Groups III and IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the antibody of Group III and the Prf amino acid sequence of Group IV appear to be separate, distinct and unrelated chemical entities. Therefore, Groups III and IV do not share a special technical feature.

Accordingly, the claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept.